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RECURRENT AND SO-CALLED METASTATIC GIANT CELL TUMOR*

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As information advances, it is obvious that clinical entities are established on the basis of a specific etiology, rather than on abstract classification. For this reason, as additional facts are disclosed, the time honored controversy concerning the inflammatory or neoplastic nature of giant cell tumors and bone cysts is giving place to a discussion of the actual causative processes of these lesions. The evidence presented in a previous paper [1] favored the view that these growths constitute a single entity, and that the giant cell tumor arises as an abnormal phase in the resorption of temporary bone in response to trauma, while the bone cyst presents the healing phase of the same lesion. Nevertheless, in view of the amount of attention recently directed to so-called metastatic giant cell tumors in the literature, it is necessary to present further evidence concerning a certain group of these lesions to delineate them more sharply from the bone sarcomas.

The high percentage of clinical recurrences after treatment in typical giant cell tumor speaks for the progressive nature of this disease. Among 222 cases of giant cell tumor in the surgical pathological laboratory of the Johns Hopkins Hospital there were thirty-one recurrent cases following a primary curettement, and many of these showed repeated recurrences despite surgical intervention. In three additional cases in the series, metastases to the lungs were supposedly responsible for the death of the patient.

An analysis for the reasons for such recurrences has been repeatedly made on the basis of the microscopic picture. In the literature various claims have been set forth by some who believe to see in the microscopic structure of the tumor the explanation of a more persistent and

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1. Geschickter, C. F., and Copeland, M. M.: Osteitis Fibrosa and Giant Cell Tumor, Arch. Surg. **19**:169 (Aug.) 1929.

TABLE 1.—*Cases with Clinical Features Leading to Recurrence*

P. N.	Race, Sex and Age	Location	Duration, Mo.	Symptoms	Roentgenogram	Treatment	Microscopic	Cause of Recurrence	Result
39860	.. .. ..	Radius, lower	..	.....	.....	1st curetting 2d curetting, 1927	2d oper. typical*	Shell destroyed	Recurred twice
39134	W F 40	Tibia, upper	10	.....	Bone shell intact	1st curetting, 1925 postoperative radiation	1st oper. typical	Age over 30	Living 3 years
38842	W F 36	Radius, lower	2	Pain, tumor	Shell destroyed	1st curetting, Feb., 1927 cautery, resected, April, 1928	1st oper. typical	Shell destroyed	Living 1 year
38407	W M 40	Femur, lower	24	Trauma, pain, tumor	.....	1st curetting, 1913 2d curetting, Dec., 1925	1st oper. typical 2d oper. typical	Age over 30	Living 15 years
37708	W F 31	Radius, lower	12	Trauma, pain	Bone shell destroyed	1st curetting, June, 1926 resection, Sept., 1927	1st oper. typical 2d oper. fibrous variant	Age over 30 Shell destroyed	Well 2 years
36182	W F 8	Jaw, lower	6	Tumor	Bone shell destroyed	1st resection, May, 1924 radiation, Sept., 1924 cauterization, Jan., 1925	1st oper. typical 2d oper. fibrous variant	Bone shell destroyed	Well 2 years
32991	W F 23	Jaw, lower	36	Loose teeth, tumor	Bone shell perforated	1st curetting, April, 1920 2d curetting, April, 1923 with cauterization	2d oper. fibrous variant	Bone shell perforated	Living 3 years
32028	W F 48	Radius, lower	36	Trauma, pain, tumor	Bone shell perforated	1st resection, May, 1921 2d resection, Jan., 1923	Bone healing Few giant cells	Bone shell perforated	Well 5 years
29428	W F 16	Femur, lower	24	Trauma, pain, tumor	.....	1st curetting, Feb., 1917 2d curetting, Oct., 1917 3d curetting, July, 1919 with radium	1st oper. typical	Poor curetting (?)	Well 9 years
29366	W F 19	Radius, lower	12	Tumor	Bone shell perforated	1st curetting, March, 1913 resection, June, 1914	2d oper. fibrous variant	Bone shell perforated	Well 14 years
28635	W M 25	Humerus, upper	2	Weakness, trauma, pain	Bone shell perforated	1st curetting, July, 1921 radium implanted resection, Jan., 1921	1st oper. typical	Bone shell perforated	Well 7 years
27461	W M 50	Humerus, lower	48	Trauma, tumor	Bone shell perforated	1st curetting, Nov., 1919 postoperative radiation 2d curetting, Feb., 1921 with cautery and radium	1st oper. typical, foam cells present	Bone shell perforated	Well 7 years
27289	W M 35	Femur, lower	30	Trauma, pain, tumor	Bone shell intact	Aspirated, April, 1919 1st curetting, May, 1919 with cautery 2d curetting, June, 1919 with cautery	Fibrous variant, second and third operation	Treated as osteomyelitis	Well 8 years

27288	..	..	..	Femur, lower	..	Pain, tumor	.....	Partial curetting, 1919 2d curetting, Aug., 1919 with cautery	.....	Treated as osteomyelitis	Well 2 years
20598	W	F	26	Tibia, upper	12	Trauma, pain, tumor	Bone shell perforated	1st curetting, May, 1918 with toxins 2d curetting, Jan., 1920 amputation, Dec., 1922	2d oper. fibrous variant	Bone shell perforated cortical bone sacrificed at operation	Well 5 years
20091	C	M	27	Femur, lower	2	Pain, tumor	Bone shell perforated	Aspirated, April, 1919 curetted, July, 1919 amputated, May, 1920	3d oper. typical	Treated as arthritis	Well 8 years
25889	W	F	28	Radius, lower	6	Pain, tumor	Bone shell perforated	1st curetting, July, 1917 with cautery 2d curetting, July, 1918 with cautery	1st oper. typical	Bone shell perforated	Well 3 years
24122½	W	M	33	Os calcis	9	Trauma, pain, tumor	Bone shell destroyed	1st curetting, July, 1911 infection 2d curetting, Nov., 1913 with cauterization	1st oper. typical	Bone shell destroyed	Well 15 years
14044	W	F	28	Radius, lower	..	Tumor	.....	1st curetting, 1909 amputation, 1910	1st oper. typical	No data	Well 6 years
12923	W	F	23	Fibula, upper	18	Trauma, pain, tumor	Bone shell perforated	1st curetting, May, 1911 resection, 1916	1st oper. typical	Bone shell perforated	Well 12 years
10376	W	F	25	Radius, lower	5	Trauma, pain, tumor	Bone shell perforated	Partial curetting, 1908 2d curetting, Sept., 1908	1st oper. typical	Incomplete curetting because of hemorrhage	Well 20 years
9881	W	M	25	Femur, lower	..	Pain, tumor	Bone shell perforated	1st curetting, March, 1909 resection, July, 1909	1st oper. typical	Bone shell perforated	Well 11 years
8412	W	M	29	Radius, lower	20	Trauma, pain, tumor	Bone shell perforated	Partial curetting, 1906 2d and 3d curetting, 1906 resection, Aug., 1907	3d oper. fibrous variant	Treated as tuberculosis	Well 8 years
7440	W	M	22	Femur, lower	6	Trauma, pain, tumor	Bone shell perforated	1st curetting, Jan., 1906 amputation, Sept., 1906	1st oper. typical	Bone shell perforated	Well 22 years
4558½	W	F	19	Femur, upper	..	Tumor, fracture	.....	Explored, toxins, 1899 1st curetting, 1901 2d curetting, 1902	1st oper. typical	Exploration without treatment	Well 26 years
1448	W	M	35	Tibia, upper	14	Trauma, pain, tumor	.....	Partial excision, 1896 1st curetting, Aug., 1896	Sections lost	Incomplete operation	Well 7 years

* Typical refers to a microscopic structure characteristic of benign giant cell tumor.

malignant course. More recently Goforth [2] has attempted to grade the microscopic picture to show the gradual transition of benign giant cell tumor to osteogenic sarcoma.

Microscopic studies of giant cell tumors in this laboratory have been carried out in an effort to confirm or possibly to elucidate the alleged malignant transformation of giant cell tumors. If it is true that these tumors may show a gradual transition to osteogenic sarcoma and kill by metastases, and reasons for this transition may be developed, then we have established a most valuable approach to the nature of a malignant condition so far as it applies to bone. The present conception of the giant cell tumor as a benign growth would have to be somewhat altered so far as this lesion would then present the characteristics of a presarcomatous growth. However logical the existence of such histologic gradations toward a malignant condition may appear, a survey of the data from many different sources, it will be shown, does not support such contentions.

In approaching this problem microscopic analysis alone is insufficient, and much is to be gained from a study of the physiopathologic processes underlying both effective and unsuccessful methods of treatment. For this reason the study of recurrent and metastatic giant cell tumors presented here includes a survey of all the factors related to this group of tumors including both clinical and embryologic features.

For purposes of analysis it has been found convenient to group the lesions under discussion into four groups. The first comprises microscopically benign giant cell tumors with clinical features leading to recurrence. The second group includes giant cell tumors which resemble sarcoma microscopically, with or without clinical recurrence. In the third group are placed those giant cell tumors which are associated clinically with metastases and death. The fourth group is composed of osteogenic sarcoma containing giant cells and resembling microscopically giant cell tumor. A discussion of these four groups is followed by an analysis of the clinical results following various types of treatment in over 200 giant cell tumors.

I. BENIGN GIANT CELL TUMOR WITH CLINICAL FEATURES LEADING TO RECURRENCE

In this group of lesions the original tumor was always characterized by a microscopic structure typical of the usual benign giant cell tumor. The failure of these lesions therefore to heal after a primary curetting cannot be explained on a histologic basis. A study of the twenty-six cases in this group, however (table 1), reveals that the cause of the recurrences is to be ascribed either to a poor selection in choosing the type of treatment for the individual case or to an incomplete operation.

2. Goforth, J. L.: Giant Cell Tumor of Bone, Arch. Surg. **13**:846 (Dec.) 1926.

Either the operator elected to curet a lesion that was too far advanced or at a disadvantageous age and site; or in performing the curettement, there was incomplete removal of the tumor and usually failure to follow with chemical or thermal cauterization.

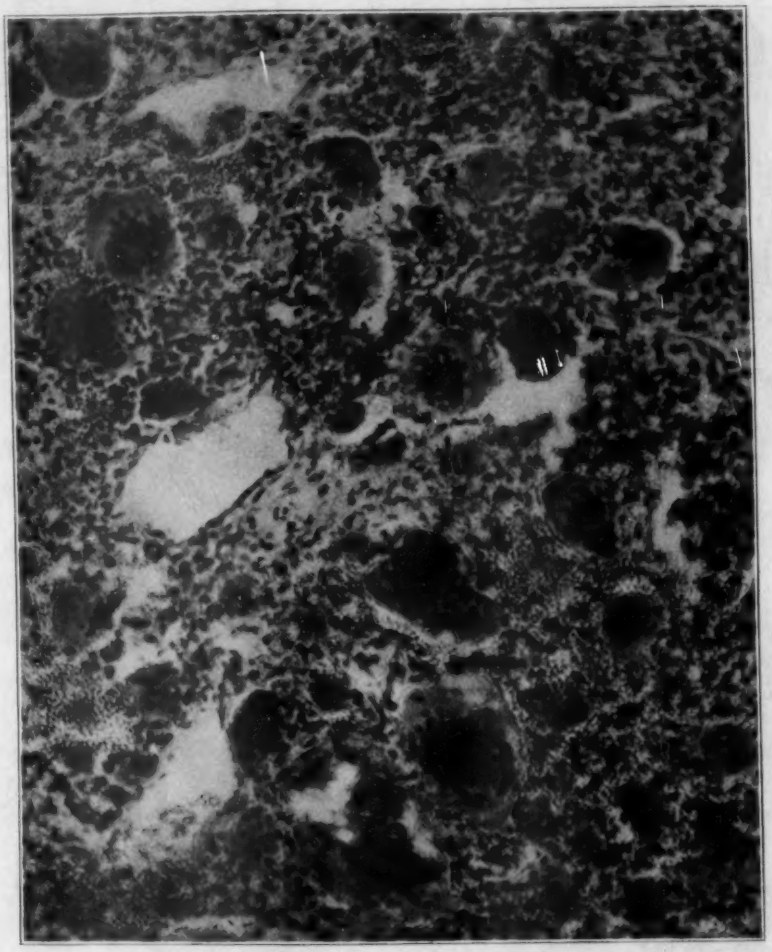


Fig. 1 (P. N. 27291, metastatic case 2).—Structure of a giant cell tumor that recurred four times. The photomicrograph shows the original lesion at the time of primary curettement, which resembles the typical giant cell tumor. Section for the photomicrograph was secured through the courtesy of Dr. B. C. Crowell from the Bone Registry of the American College of Surgeons.

Microscopic Analysis.—While some authors [3] claim to be able to distinguish in the section of the original giant cell tumor, the cause for

3. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

its subsequent recurrence, the lesions in the present group show no peculiarities in the microscopic picture which would bear out such a claim. Tissue taken from the original lesions in the twenty-six cases already referred to shows a predominance of large multinucleated giant cells, which average over 30 to the low power field and contain

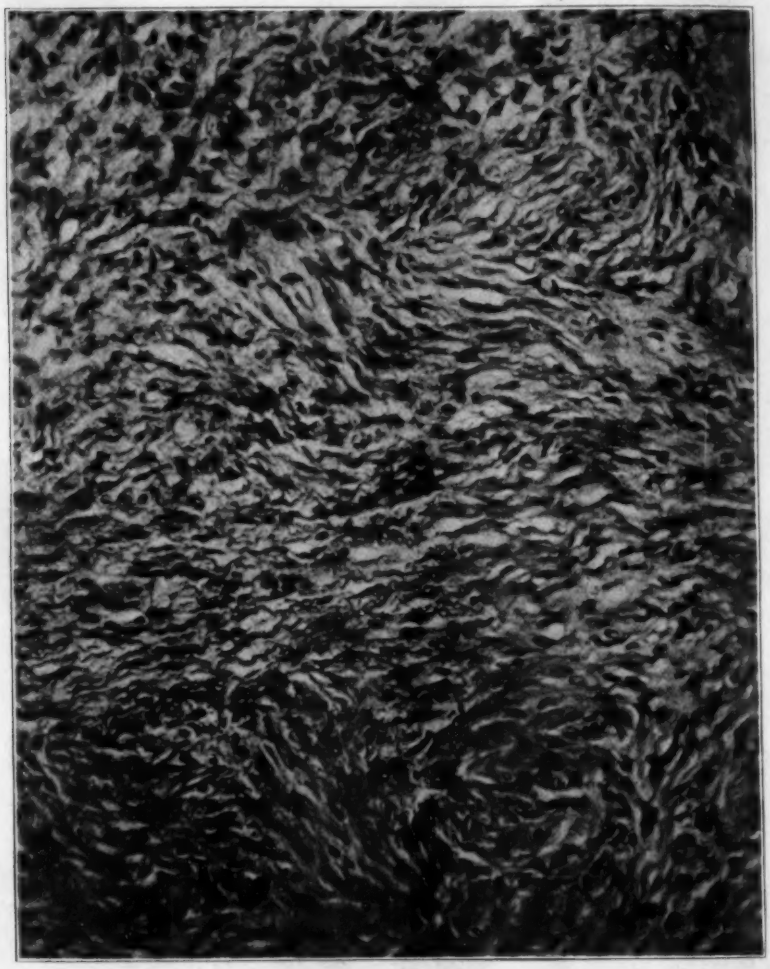


Fig. 2 (P. N. 27291, metastatic case 2).—Photomicrograph of the same tumor shown in figure 1, after the fourth operation. The unusual amount of fibrous proliferation is due to a healing reaction, but was incorrectly diagnosed sarcoma by many competent pathologists. The healing reaction has been accentuated by roentgen and radium therapy.

from 15 to 200 nuclei per cell (fig. 1). These giant cells are embedded in the round cell stroma typical of all benign giant cell tumors, and in the sections taken from the second operation after the tumor has recurred,

there is no histologic change toward osteogenic sarcoma or what may be called a malignant giant cell variant. Unless the lesion has become infected, the histologic change following recurrence is usually characterized by an increase of fibrous tissue (fig. 2). Numerous spindle cells and fibroblasts are found among the round cells indicating nature's attempt at a healing reaction. Occasionally, foam cells are found in the sections, and although this entitles the lesions to the name of xanthoma variants, there is no significant change in the typical microscopic struc-

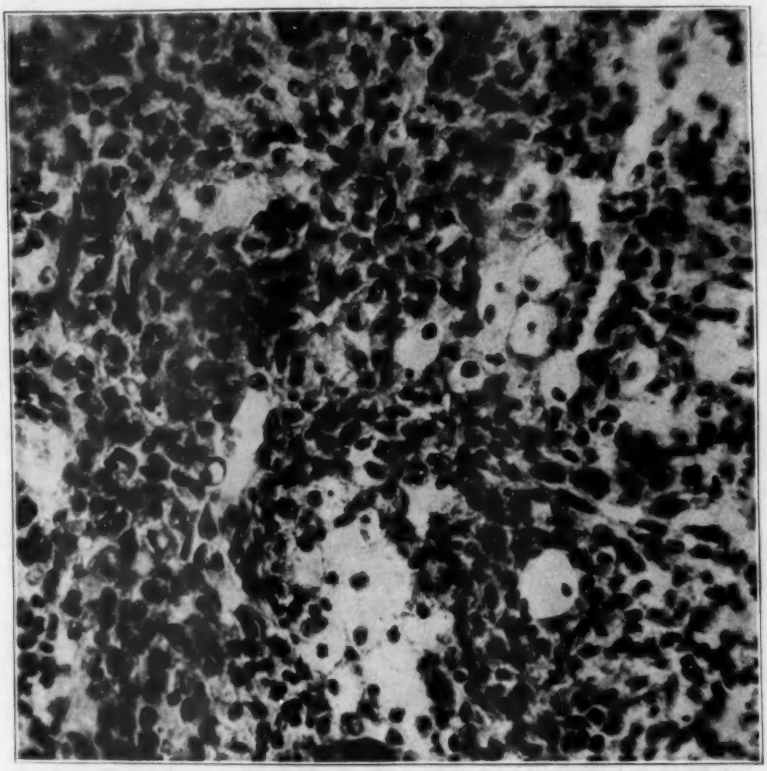


Fig. 3 (P. N. 27461).—Foam cells in a typical giant cell tumor that recurred. These so-called xanthoma cells are the result of extension by the tumor into the soft parts.

tures (fig. 3). It is important to emphasize here, as well as elsewhere, that we believe that such foam cells are associated with perforation of the bony capsule and extension of the tumor into neighboring soft parts which furnish the lipoids characteristic of these xanthoma cells.

Since the microscope is of no aid in disclosing the reasons for recurrence in this group of tumors, it is necessary to look into the clinical features of the growth and the methods of treatment in order to explain

the failure of these tumors to follow the usual course and heal after a primary curettement.

Clinical Features Leading to Recurrence.—A review of the clinical features of this group shows that age must be considered as a contributory factor to recurrence. In order to determine the importance of this factor, 105 cases in which the patients were submitted to primary curettement were selected, and the ages of those in whom curettement

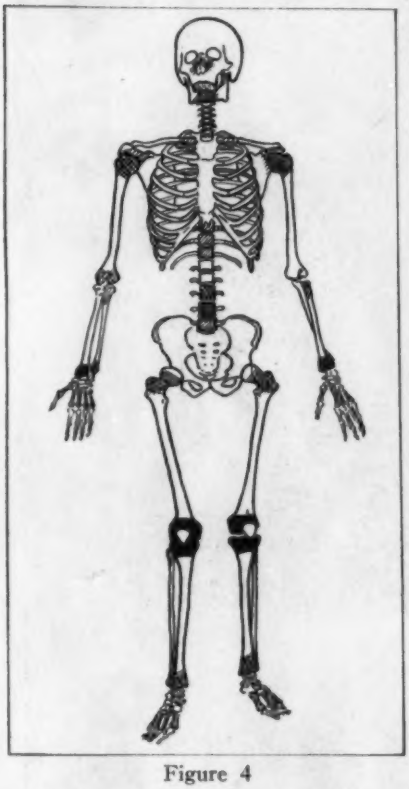


Figure 4

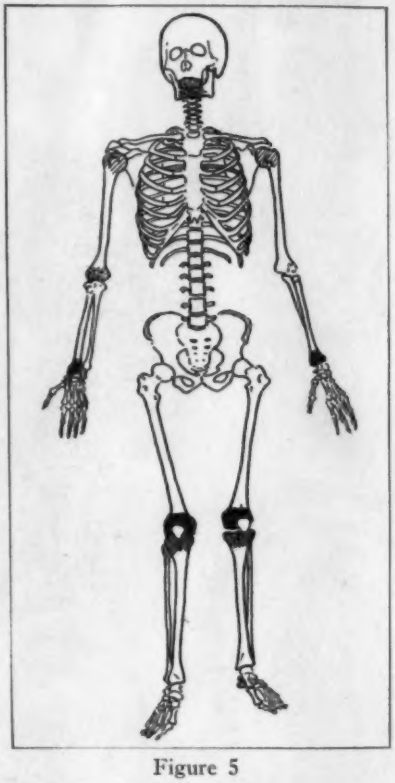


Figure 5

Fig. 4.—Chart showing the skeletal sites involved by 222 giant cell tumors. The solid black area indicates the most frequent sites; the checked areas, the common sites, and the diagonal lines, the occasional sites. Other sites are exceedingly rare. Note that the epiphyseal regions are most often affected.

Fig. 5.—Chart showing the skeletal sites involved by thirty-one recurrent giant cell tumors. The solid black area indicates the most frequent sites; the checked areas the common sites; and the diagonal lines the occasional sites (compare with fig. 4).

was successfully done were compared with the ages of those who suffered recurrence. In the group of patients with giant cell tumors cured by curetting, 21 per cent were over 30, and 41 per cent were under 21. In the recurrent groups of giant cell tumor, 42 per cent were over 30 years

of age and only 16 per cent were under 21. There is, therefore, a contrast between the ages in the recurrent and in the nonrecurrent groups with a definite tendency for the giant cell tumor to recur more readily in persons more than 21 and even more frequently in those more than 30 years of age. This is to be explained by the fact that cortical bone declines in its power to heal and ossify after the age of 21, and as we have pointed out previously, this cortical bone is a primary factor in the healing reaction about a giant cell tumor.

The location of the tumor is also of some significance in regard to recurrence. While recurrent giant cell tumors occur in most of the sites where giant cell tumors arise, the lower end of the radius appears to be a favorite location for the return of the lesion after curetting (figs. 4

Fig. 6 (P. N. 37708).—Roentgenogram of a giant cell tumor of the lower part of the radius showing extensive destruction of the bone shell which led to a recurrence of the tumor after curetting.

and 5). The ordinary giant cell tumor affects most frequently the upper part of the tibia, and the lower part of the femur and of the radius. The upper part of the tibia shows relatively few recurrences (8 per cent) and the lower part of the femur a moderate number (39 per cent), while in a series of sixteen curettings in the lower part of the radius, 50 per cent recurred. The explanation of these frequent recurrences in the radius lies in the destruction of the bone shell, which usually has progressed to a further degree in this nonweight-bearing bone than in the bones of the leg before the patient is aware of severe symptoms in the use of the limb. The average duration of symptoms is twenty months in the radius compared with fourteen months for the usual giant cell tumor (fig. 6).

Both age and the site of recurrences emphasize the influence of cortical bone in the healing of giant cell tumor after curettement.

Primarily, the most valuable asset in the cure of a giant cell tumor is the preserved shell of cortical bone with an intact and competent vascular supply. This is evidenced by the spontaneous healing of giant cell tumors to produce a bone cyst in the metaphysis and shaft of the long bones in which there is a substantial layer of cortical bone with a richly vascularized subperiosteal mantle. The origin of the abnormal growth is dependent on the temporary dysfunction of this portion of the bone following a trauma.

Roentgenograms and gross specimens emphasize that the giant call tumor most frequently recurs because curettement rather than resection has been undertaken in a tumor that has destroyed too much of the bone shell before the time of surgical intervention (figs. 7 and 8). The

Fig. 7 (P. N. 32924).—Roentgenogram of a giant cell tumor in the lower end of the fibula, similar to the case shown in figure 6. Advanced destruction of the shell of cortical bone was responsible in all probability for the recurrence after curettement in this case.

perforation of a giant cell tumor into the soft parts is more to be feared because of the cortical destruction antecedent to the perforation than because of infiltration and the danger of incompletely removing the soft part tumor (table 1).

Treatment so far as it involves the selection of the type of operation in any particular case and also the skill with which such therapy is applied constitutes the major cause for recurrences. Obviously, curettement in a patient over 35 years of age with a giant cell tumor in the lower end of the radius that has destroyed the major part of the bone shell invites recurrence. Resection with subsequent transplantation of bone is to be preferred. In this way the selection of the mode of treatment determines the clinical result. In an equal number of cases the

failure to use chemical or thermal cauterization after curettement predisposes to recurrence. In seven of the cases in this series the recurrence of the tumor could be ascribed to partial curettement. Usually the failure to remove all of the tumor was due to an erroneous diagnosis which led to simple aspirations or to incomplete excision, in the belief that a suppurative condition existed. In one case the operation was incomplete because undue hemorrhage was encountered.

Fig. 8 (P. N. 32924).—Gross specimen of the tumor shown in figure 7. The shell is perforated and infection followed (fig. 11).

In curetting care should be taken to remove as much of the cancellous bone involved as possible, and at the same time to preserve a maximum amount of the cortical bone shell with intact blood supply. When the surgeon is over liberal in the removal of cortical bone, repeated operation is often necessary, and each time more and more of the cortical bone is sacrificed, until cure by curettement becomes impossible.

The fact that no giant cell tumor has recurred after primary radical resection or amputation emphasizes the fact that the mode of treatment and not the histology of the tumor is the primary factor in recurrence.

As Bloodgood [4] has repeatedly pointed out, the typical giant cell tumor is benign, and conservative treatment by efficient curettement and cauterization is the operation of choice in most instances. This is particularly true when resection because of the bone involved would be equivalent to amputation. But in elderly patients and in cases in which much of the bone shell is destroyed and in sites such as the fibula, radius and humerus when resection with transplant of bone will restore function, discrimination between curettement and resection should be carefully made, and the possibilities of preliminary treatment by roentgen therapy seriously considered. Because of the close relationship of these lesions to the usual bone cyst, the possible benefits resulting from collapsing the cavity remaining by crushing [5] or by filling with bone chips, must also be weighed.

II. MALIGNANT VARIANTS AND DIFFERENTAL MICROSCOPIC DIAGNOSIS IN GIANT CELL TUMOR

In the cases considered in this group, seven lesions are grouped together which showed under the microscope characteristics resembling osteogenic sarcoma (tables 2 and 3). Practically all of these cases were submitted to various pathologists for diagnosis, and in most instances there was a striking lack of agreement among those most competent to judge. Although ultimate clinical results favor the conclusion that the tumors were benign (no deaths are recorded in the follow-ups), still in three instances (P.N.29327, P.N.39404, P.N.26792) the microscopic structure is indistinguishable from certain varieties of osteogenic sarcoma.

This small group of cases selected from among 222 cases of giant cell tumors of bone demonstrates practically all the points of confusion arising in the differential microscopic diagnosis of giant cell tumor. All the important variations in the histologic picture of this tumor are depicted, such as changes due to necrosis from poor fixation, alterations dependent on recurrence and infection, modifications due to partial healing with fibrosis, changes brought about by irradiation or by infiltration of adjacent tissues, as well as the actual presence of osteogenic sarcoma in the sections. An analysis, therefore, of this small group of so-called malignant variants of giant cell tumor serves admirably as a study in the differential diagnosis of this growth, as far as microscopic changes are concerned. It serves to emphasize the importance in microscopic diagnosis of a familiarity on the part of the pathologist with changes produced in the histology of giant cell tumor by previous operations,

4. Bloodgood, J. C.: The Conservative Treatment of Giant Cell Sarcoma, Ann. Surg. **56**:210, 1912.

5. Henderson, M. S.: Giant Cell Tumor of the Upper End of the Femur. Minnesota Med. **11**:542. 1928.

TABLE 2.—*Malignant Variants of Giant Cell Tumor with Recurrence*

P. N.	Race, Sex and Age	Location	Duration, Mo.	Symptoms	Roentgenogram	Treatment	Microscopic	Cause of Microscopic Change	Result
36170	W F 32	Lower jaw	12	Tumor	Bone shell intact	Partial curetting, 1923 by dentist 2d curetting, Oct., 1924	2d oper. young fibrous tissue with new bone	Healing after 1st operation	Well 3 years
32924	W M 12	Fibula, lower	3	Trauma, pain, tumor	Bone shell perforated	1st curetting, April, 1923 2d curetting, May, 1923 with cauterization resection, Aug., 1923	1st oper. necrotic tissue* 2d oper. infected tissue 3d oper. infected tissue	Necrosis and infection	Well 5 years
29327	W M 19	Femur, lower	4	Trauma, tumor	Bone shell intact	Exploration, Oct., 1920 followed by infection 1st curetting, Nov., 1921 with cauterization amputation, 1922	2d oper. infected tissue 3d oper. malignant variant Section indistinguishable from osteogenic sarcoma	Infection	Well 6 years
25892	W M 30	Humerus, upper	24	Trauma, pain, tumor	Bone shell intact	Partial curetting, 1916 2d curetting, July, 1916 3d curetting, July, 1920	2d oper. infectious changes	Infection	Well 8 years
25842	C M 49	Vertebrae	18	Pain, tumor	.....	Partial excision, 1919 Further excision, 1919 Further excision, 1920	3d oper. infectious changes	Infection	No follow-up

* In this table malignant variant refers to microscopic change dependent on recurrence in every instance but this.

irradiation, partial healing, infection, invasion of soft parts and poor fixation; in comparison with the typical structure of both giant cell tumor and osteogenic sarcoma.

Clinical Features.—The clinical features of these "malignant" variants are given in tabular form in tables 2 and 3. It will be seen that five of seven cases recurred after initial treatment of curetting or excision, and that the microscopic variations are generally associated with a second or third operation with intervening infection. In other words, instead of the so-called malignant microscopic structure being the cause of the recurrence, the reverse is true—the infection of the recurrent tumor is usually the cause for the microscopic change. Death has not been recorded in any of the seven cases, but in table 2, two patients alive, five and six years after treatment, respectively, were subjected to resection or amputation, and such treatment which may result in cure

TABLE 3.—*Malignant Variants of Giant Cell Tumor Without Recurrence or Metastasis*

P. N.	Race, Sex and Age	Location	Duration Mo.	Symptoms	Roentgenogram	Treatment	Microscopic	Result
39484*	W F 15	Scapula, neck	6	Pain, tumor	Shell intact	Curetted, July, 1927	Calcified cartilage in the malignant variant	Well 1 yr.
26792*	W M 16	Humerus, upper	16	Trauma, pain	Shell thin perforated	Curetted, Oct., 1920, with cauterization, radium and toxins	Calcified cartilage in the malignant variant	Well 8 yr.

* See P.N. 35226 and P.N. 40872, included with metastatic giant cell tumors and microscopically identical with these two cases.

in genuine sarcoma must be considered in evaluating the character and clinical course of the growth. In table 3, both patients for whom data are given are in the sarcoma age. The tumor did not recur after curretting in either case, but the resemblance to a form of osteogenic sarcoma observed in the original tumors is sufficient to make the diagnosis of giant cell tumor exceedingly doubtful.

Microscopic Analysis.—In the cases listed in table 2 all of the lesions recurred, and unfortunately verified sections from the original tumors were obtained in only one instance. The condition in all five cases was diagnosed osteogenic sarcoma by the majority of the pathologists passing on the sections. In the case in which sections from the first operation were seen (P.N.32924), poor fixation resulting in necrosis was responsible for the inability to distinguish between sarcoma and a variant of giant cell tumor (fig. 9). In the other four cases, owing to lack of knowledge of the history or to actual errors in the clinical or clerical records, the pathologist making the diagnosis was not informed that he was looking at a recurrent lesion and not the original tumor. In one

case (P.N.36170) a marked healing reaction resembled fibrosarcoma, and in the other three cases (table 2) infection accounted for the marked pyknosis and cloudy swelling of the nuclei mistaken as a feature of osteogenic sarcoma. Unfamiliarity with the changes in giant cell tumor produced by partial healing after a primary operation or by infection was therefore the cause for most of the diagnostic errors in this group.

In the case in which marked healing reaction occurred (fig. 2), a careful study of the sections under a high power lens showed that the

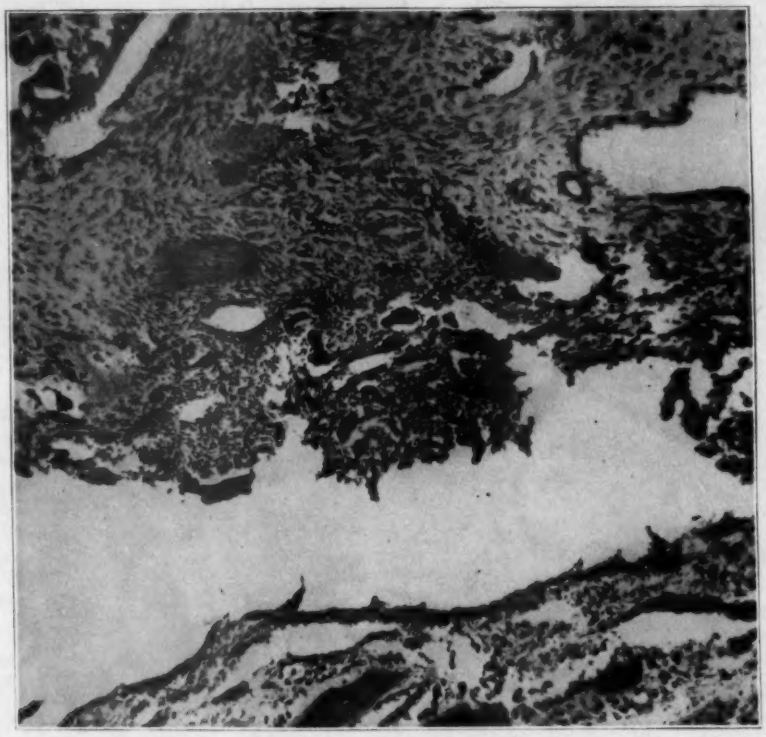


Fig. 9 (P. N. 26091).—Photomicrograph of a poorly fixed specimen of giant cell tumor. Necrosis similar to this led to an erroneous diagnosis of sarcoma in case P. N. 32924.

young proliferating cells were early fibroblasts participating in a reaction referred to by us as fibro-ostosis.[1] In the cases in which the patients were previously infected, the pyknosis and cloudy swelling resulting simulated malignancy, particularly when examination was made under high magnification (fig. *A* and fig. 11, ARCH. SURG., vol. 19, pp. 172 and 202, respectively). The pyknosis resembled early mitosis so often seen in sarcoma, and the swollen nuclei undergoing degeneration resembled the large pale nuclei seen in a malignant condition of the bone. The

low magnification is perhaps more reliable in arriving at a trustworthy conclusion. When thus examined there was more loose fibrous tissue, a less cellular stroma and more nuclear débris than is seen in sarcoma under lower magnification. The giant cells present in these malignant variants were larger and more numerous and contained over 15 nuclei to the cell, which is not typical of osteogenic sarcoma. Analysis under high power magnification of the large vesicular nuclei in these infected cases showed that often they were composed of several smaller nuclei which were undergoing clumping and losing the finer markings of their former structure, with the gradual formation of an amorphous mass.

Fig. 10 (P. N. 32924).—The granulating wound of the tumor shown in figures 7 and 8.

In any case, therefore, in which a bone tumor containing frequent large giant cells averaging over 15 nuclei per cell is seen with evidence of round cell and polymorphonuclear infiltration and frequent areas of hemorrhage surrounded by young loose fibrous tissue, the pathologist should be on his guard against making a diagnosis of sarcoma and wary lest the apparent malignancy of the nuclear material is in reality pyknosis and cloudy swelling dependent on infection and degeneration (Bloodgood [6]).

In table 2 there is one exception to this rule (P.N.29327). The tumor in the lower part of the femur of a white man, aged 19, was

6. Bloodgood, J. C.: Why Do Giant Cell Tumors Recur? To be published.

explored after symptoms of four months' duration following trauma. The original diagnosis was giant cell tumor, but microscopic examination was not made, and the wound was allowed to become infected. Sections from a curetting performed a year later (fig. 12*A*) showed the malignant variant due to infection, but sections from a subsequent recurrence which led to amputation one year later showed unquestionable osteogenic sarcoma (fig. 12*B*). The patient is alive and well six years

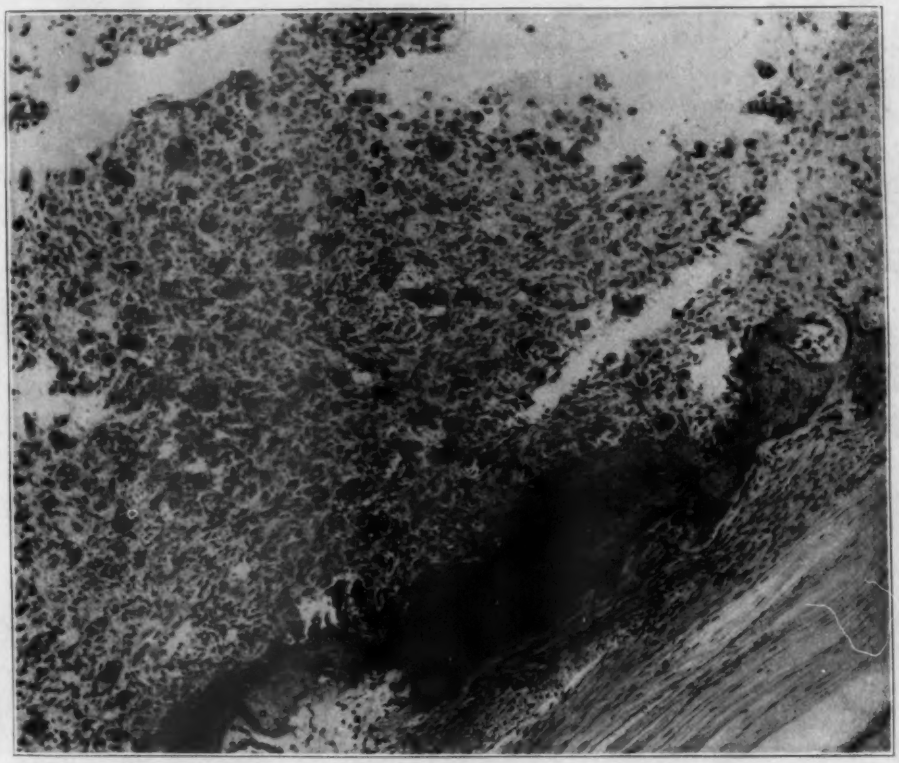
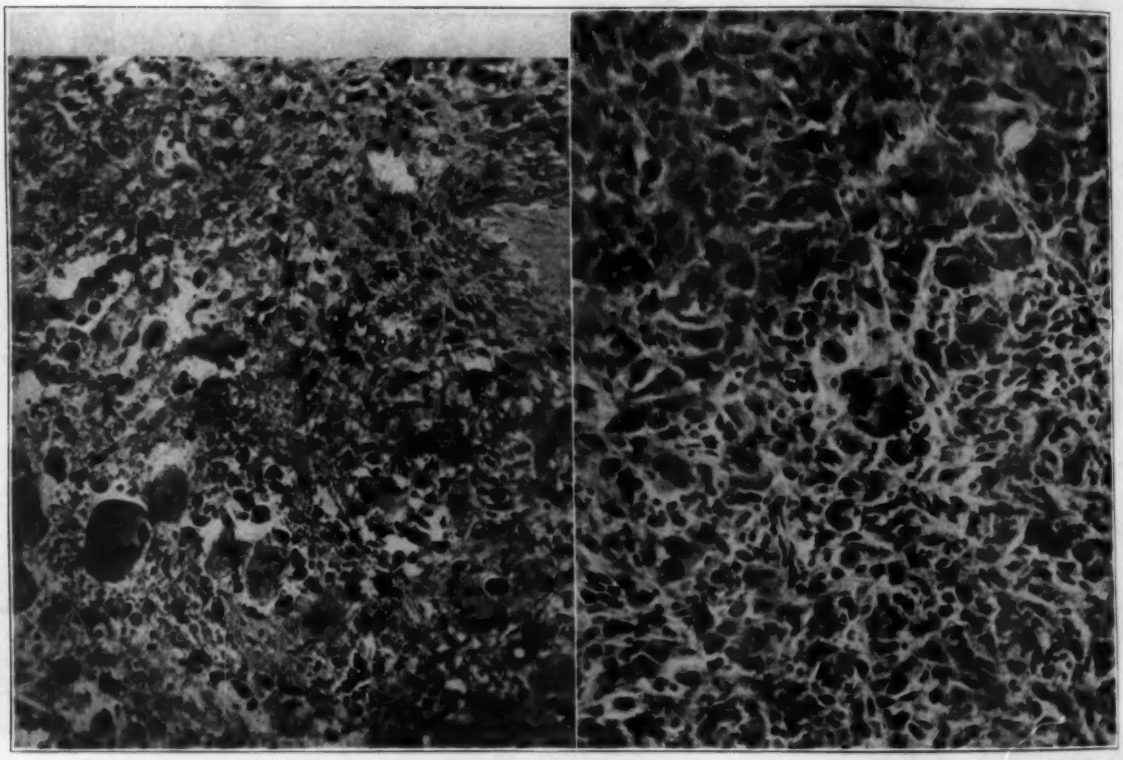


Fig. 11 (P. N. 32924).—Low power photomicrograph of the tumor shown in figures 7, 8 and 10. Infection has occurred resulting in the so-called malignant variant. Pyknosis and cloudy swelling of the nuclei resemble the cells seen in osteogenic sarcoma.

after amputation, but this must be looked on in all probability as an amputation cure in sarcoma. When this case is compared with those in Section III of this paper, it warrants consideration as a case of sarcomatous transformation in a giant cell tumor. But the sections of the original exploration are not available, and those from the second observation are atypical and cannot be proved to be benign; whereas the failure of the lesion to heal after infection might well have stimulated

a second neoplastic process of sarcomatous nature. The matter will be discussed further under the metastatic group of giant cell tumors. This case was included in table 2 because the patient is living and is without signs of metastases.

Although the age of the patients, the clinical course and the microscopic structure of the tumors in the two cases listed in table 3 are typical of a chondroblastic form of osteogenic sarcoma, giant cells are present



A B

Fig. 12 (P. N. 29327).—*A*. Photomicrograph from the second operation on an alleged malignant variant of giant cell tumor. Infection has occurred, and early osteogenic sarcoma is simulated by the large swollen nuclei. Note the unusual amount of nuclear débris. *B*. Photomicrograph from the third operation on the same tumor as shown in *A*. This section is indistinguishable from osteogenic sarcoma.

in the sections, and both patients are alive after curetting, without signs of recurrence. In one case (P.N.39484) only one year has elapsed since operation, and the ultimate result may confirm this as sarcoma, but in the other case with similar microscopic structure, the patient (P.N.26792)

is living eight and a half years after curetting followed by deep roentgen and radium implantation, in addition to erysipelas and prodigiosus toxins (Coley).

In this last case (figs. 13, 14 and 15) which is the well known case of Dr. Bunts of Cleveland, the patient had a lesion in the upper part of the humerus which was originally diagnosed sarcoma by most of the pathologists who saw the sections, with a minority dissenting in favor of giant cell tumor. Despite the fact that the survival of the patient has swung the pendulum of opinion to a diagnosis of "malignant variant" of giant cell tumor, a study of over thirty cases of similar microscopic structure shows the lesion to be a malignant grade of osteogenic sarcoma. The cure must be ascribed to the radium and roentgen treatments.

Fig. 13 (P. N. 26792).—Roentgenograms of a lesion originally diagnosed sarcoma and then giant cell tumor of the so-called malignant variant type which must now be classed as a form of chondroblastic sarcoma. Note the periosteal lipping at the lower margins of the tumor and the fuzzy periosteal reaction. There is no maximal area of bone destruction immediately beneath the cortex as in giant cell tumor. The roentgenogram on the right shows radium implantation in the tumor.

The form of "malignant variants" shown in table 3, therefore, we believe subject to reinterpretation. Under the microscope these tumors show a rapidly proliferating and early form of cartilage cell which produces only an abortive form of chondromatrix transformed here and there by calcification (fig. 14). The giant cell areas invading the tumor represent, it would seem, an attempt on the part of the normal bony structures to vascularize and resorb this malignant tissue by a process typical of the resorption of normal calcifying cartilage in the human embryo.[1] This point will be brought out again in this paper in discussing "metastatic" giant cell tumors. Suffice it to say at this point that in

making a microscopic diagnosis of giant cell tumor the pathologist must be on his guard, not only against labeling benign infected giant cell tumors sarcoma, but also against calling this type of sarcoma showing giant cell areas, a benign tumor.

For the purpose of completing a differential diagnosis we shall revert briefly to the question of xanthoma variants of the giant cell tumor, since certain authors consider these among the malignant variants of giant cell tumor (fig. 3). The view taken here is that the foam cells

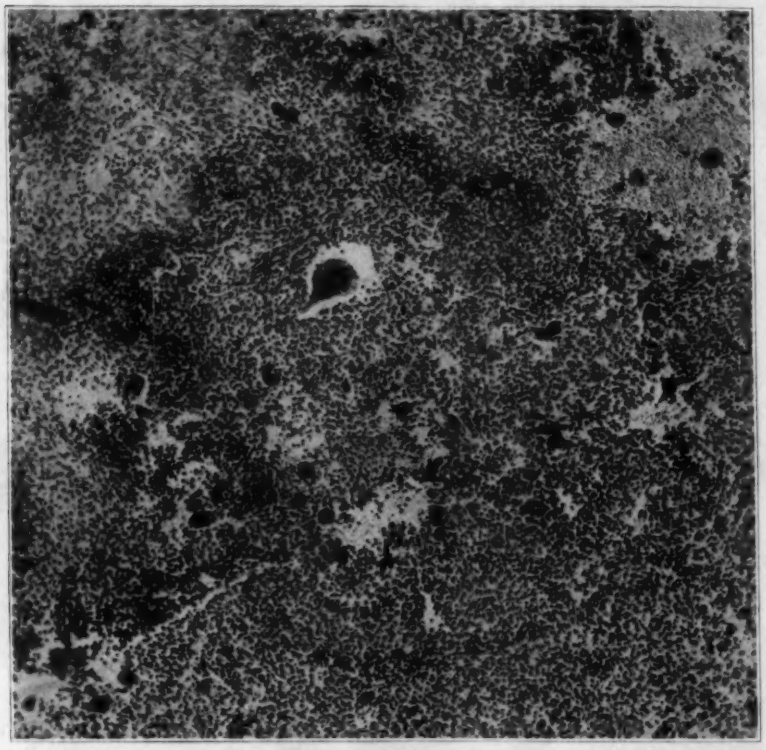


Fig. 14 (P. N. 26792).—Low power photomicrograph of the tumor shown in figure 13. Note that in addition to the giant cells, there is a cartilaginous matrix undergoing calcification in the upper portion of the picture which is better seen in figure 15.

are the result of a perforation of the bone shell, and in themselves indicate nothing more than that the tumor has reached the soft parts. They signify nothing in regard to the anaplastic tendencies of the tumor and are independent of its essential components.

In summarizing this study of the "malignant variants" of giant cell tumor, two questions of long standing may be answered. First, what is the relation of the microscopic picture of a "malignant variant" to recur-

rence after curetting, and second, what is the relation of the "malignant variant" of giant cell tumor to osteogenic sarcoma.

In answer to the first, it may be said that "malignant" modification in the microscopic structure of a giant cell tumor is usually the result and not the cause of recurrence. When the "malignant variant" structure is primary and recurrence results, metastasis is apt to follow, showing that in a few instances a genuine sarcoma has been masquerading under the false diagnosis of giant cell tumor.

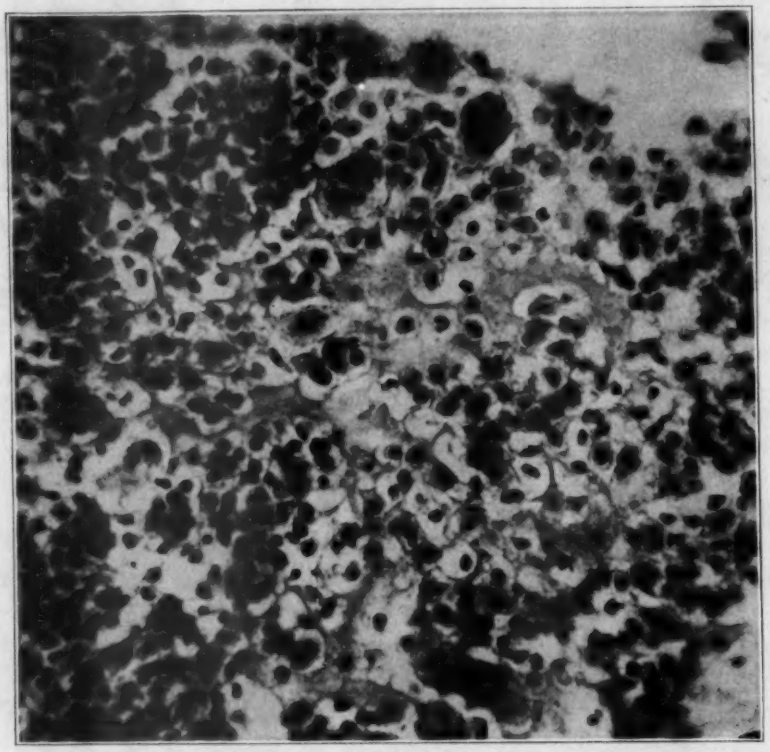


Fig. 15 (P. N. 26792).—High power photomicrograph of the cartilaginous area shown in figure 14. This type of cartilaginous matrix has never been observed in any of the benign giant cell tumors in our series of over 200 cases.

And on this score, in answer to the second question, of the relation of such sarcomas to giant cell tumors we may say that the giant cell phase of osteogenic sarcoma is usually a secondary process in which giant cells are invading malignant areas of chondroblastic sarcoma in response to the abortive calcified cartilage present. Here the cartilaginous bone is primary and the giant cell areas secondary. In benign giant cell tumor the giant cell areas are primary and are secondarily invaded by bone, not of a cartilaginous variety, but of fibroblastic origin.

From the point of view, therefore, of differential diagnosis, the question to be decided is the type of new bone formation present. The abortive chondroblastic type signifies sarcoma.

III. THE METASTATIC GROUPS

Recently there has been an attempt to show that the typical giant cell tumor called benign may occasionally metastasize and produce death. Stone and Ewing,[7] Goforth,[8] and Finch and Gleave [8] are among others who have published reports of unusual giant cell tumors, apparently typical in structure, but peculiar in behavior. Goforth stated that "an occasional case is met with, which although locally malignant, and in a few instances actually metastasizing, apparently does belong to the giant cell tumor group." Similar statements are frequently occurring in the literature with illustrative case reports, and it would seem that there is a tendency for the pendulum to swing away from the more fundamental contributions of Nélaton,[9] Paget [10] and Bloodgood [11] on the benign nature of the giant cell tumor.

Since the fountain head for such statements on the admittedly unusual behavior of these tumors is to be found in the cases reported, the determination of their veracity must be made by an analysis of the cases cited. We have gathered eight such cases from the literature and from the records of the surgical pathological laboratory of the Johns Hopkins Hospital. The value of the material thus gathered depends on the facts that we have the actual sections available for study on all of these cases kindly sent to us from various clinics, and that the eight cases analyzed subsequently represent the unusual members of a much larger series from the clinics of New York, Philadelphia, Chicago, Baltimore, Canada and England—in all a series of well over 500 cases.

Two important conclusions stand out in analysis of this material: First, in no case has a nodule of typical giant cell tumor ever been found in the lung, for wherever these metastatic nodules have been examined, they have shown the histology of osteogenic sarcoma (fig. 21). Second, in no one case has the association of an originally benign and typical giant cell tumor in the bone with a secondary metastatic osteogenic sarcoma in the lung been proved.

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7. Stone, W. S., and Ewing, J.: An Unusual Alteration in the Natural History of a Giant Cell Tumor of Bone, Arch. Surg. **7**:280 (Sept.) 1923.

8. Finch, E. F., and Gleave, H. H.: A Case of Osteoclastoma with Pulmonary Metastasis, J. Path. & Bact. **29**:399, 1926.

9. Nélaton, E.: Tumeurs benignes des os, Paris, 1860.

10. Paget, J.: Surg. Path., Philadelphia, Lindsay & Blakiston, 1854, Lecture 27, p. 446.

11. Bloodgood, J. C.: Benign Bone Cysts, Osteitis Fibrosa, Ann. Surg. **52**:145, 1910.

These are the two fundamental points brought out subsequently. On the whole, pathologists are agreed that regardless of their opinion as to the nature of the original growth, the actual metastasizing lesion is not giant cell tumor but an osteogenic sarcoma. It may be taken as proved that a giant cell tumor found to be typical by a competent pathologist is safely treated conservatively. The question, therefore, is not whether a giant cell tumor will metastasize—it never does—but whether these growths when they recur after improper treatment will undergo malignant change and give rise to osteogenic sarcoma. This question has not been settled, but the evidence brought forth subsequently would seem to answer it in the negative.

The eight cases to be considered are reviewed in abstract and divided into three groups. All of the cases were studied in one or more phases, microscopically, by the authors. All were followed clinically and all terminated in death. In group 1 (two cases), careful inquiry into the nature of the death has shown the cause of the fatality to be other than neoplastic, and metastases were erroneously considered to have occurred. In group 2 (four cases) the nature of the primary lesion was never adequately proved. It was, however, evidently benign in each case, and was followed eventually—*after an interval of years*—by a sarcoma with metastases. In group 3 (two cases) the microscopic structure, the brief clinical course and the nature of the death, all point to a primary sarcoma of bone erroneously diagnosed as a benign giant cell tumor.

The key to the analysis in this group of cases is to be found in a proper understanding of the fundamental pathologic processes of both giant cell tumor and osteogenic sarcoma in relation to the embryology of bone. We consider the point well established that giant cell tumor tissue represents an exaggerated normal phase of the resorptive ("osteoclastic") process in the production of bone from cartilage (Geschickter and Copeland [1]). We also will endeavor to show in a subsequent article, based on the study of 400 cases of osteogenic sarcoma that this group of tumors rehearses in its various phases the embryology of normal bone, and therefore there will be present at times the osteoclastic or resorptive stage of temporary bone characterized by the presence of giant cells. It is thus evident why on further analysis supposedly malignant giant cell tumors so often turn out to be merely areas in which a bone-forming sarcoma exhibits a resorptive phase marked by giant cells typical of the histogenesis of normal bone via the cartilaginous route.

The first two cases (1 and 2) in group 1 were both erroneously placed in the metastatic group, since on final analysis it was found that the patients died of causes other than tumor.

REPORT OF CASES

CASE 1 (P. N. 34402; fig. 16; Dr. W. G. Turner and Dr. T. R. Waugh[12]).—*Bone tumor; giant cell; femur, lower end, left; metastatic (?) to femoral vein: dead from pulmonary embolism.*

History.—Frank W., a white man, aged 41, patient of Dr. Turner and Dr. Waugh, was admitted to the Royal Victoria Hospital, Canada, complaining of trauma which had occurred five months previously, after striking the left knee on a piece of stone. Pain and swelling with limp had been present for four months and swelling of the thigh and groin for three weeks. He was admitted to the orthopedic service of the Royal Victoria Hospital on May 31, 1922.

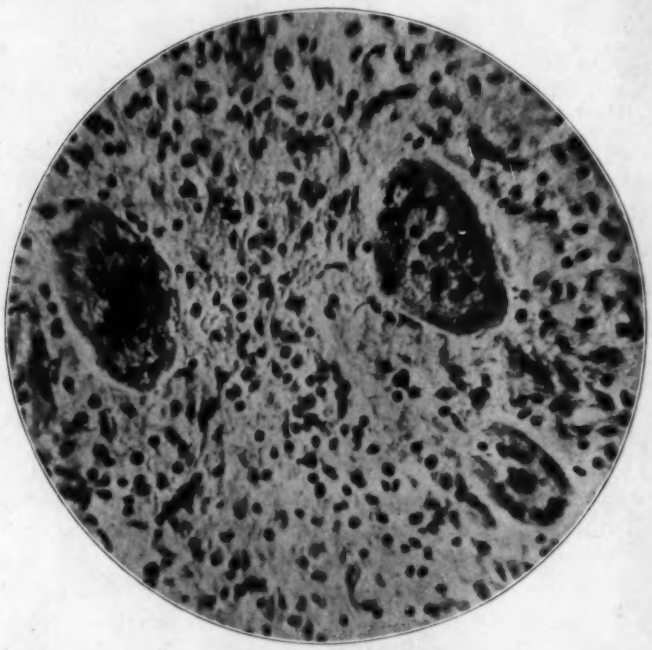


Fig. 16 (P. N. 34402, metastatic case 1 of Dr. Turner and Dr. Waugh).—Giant cell tumor with spindle cell stroma in a venous thrombus occurring in the wall of the femoral vein at the groin. Photomicrograph reproduced from the article of Dr. Turner and Dr. Waugh through the courtesy of the authors.

Examination and Course.—The entire left leg was hard, edematous and swollen. Roentgen examination showed perforation of the bone shell, partial destruction of the epiphysis and a tumor encapsulated by periosteum. The lungs were clear.

Roentgen treatment was begun in March, 1922, and continued for six weeks. On June 8, 1922, the leg was amputated at the hip joint. Microscopic examination made by Dr. Bloodgood revealed giant cell tumor with spindle cell stroma in a thrombus. The patient died six months after injury. On July 8, 1922, pulmonary embolism was found at necropsy, but no metastases of the lung were found.

12. Turner, W. G., and Waugh, T. R.: Am. Surg. **78**:846 (Dec.) 1923.

Comment.—Venous and pulmonary involvement and death were embolic in nature and not metastatic, to be ascribed to accidental causes and not to the malignant condition of the tumor. In all probability the duration of symptoms was longer than was recalled by the patient.

CASE 2 (P. N. 27291, figs. 1 and 2; JCB No. 10290; Dr. P. D. Wilson).—*Bone tumor; giant cell; radius, lower end; recurrent; dead of cardiac failure at 70 years.*

History.—Mrs. K., a white woman, aged 68, a patient of Dr. P. D. Wilson, Boston, complained of pain and aching in the wrist of two or three months' duration, beginning in April, 1920. The pain was worse on motion.

Examination and Course.—The lower end of the forearm was swollen chiefly on the radial side and on the dorsum. On March 23, 1922, roentgen examination showed the bone shell almost completely destroyed and no trabeculae. On June, 1923, examination revealed complete destruction of the lower part of the radius. The first operation was performed on July 29, 1920. Partial curettement was performed. A putty-like material was removed. Bleeding was profuse. The wound was packed with gauze and drained, and roentgen treatment was begun. On Nov. 30, 1920, the second operation was performed by Dr. Simmons and Dr. Wilson. Tissue like current jelly was curetted. There was no chemical or thermal cauterization at either operation. Radium seeds were placed in the cavity and radium tubes at the wound entrance. On March 2, 1922, curetting was done and roentgen treatment was administered. On July 23, 1922, curetting was again performed. On Sept. 23, 1922, the arm was amputated.

The specimen removed at the first operation showed typical giant cell tumor. The condition was diagnosed by Dr. Bloodgood. The specimen removed at amputation revealed marked fibroblastic proliferation. The condition was diagnosed sarcoma by many pathologists. On Oct. 23, 1922, the condition recurred in the stump. On Nov. 23, 1922, the patient complained of pain in the back. On Dec. 23, 1922, two years and eight months after the first symptoms occurred, the patient died of pneumonia (probably pulmonary metastases?) and cardiac failure.

Comment.—The original tumor was unquestionably a benign giant cell tumor of which sections are available (fig. 1). Repeated recurrences can be ascribed to partial curettement in the first instance, the age of the patient and the marked destruction of the shell of cortical bone. The sections from the amputated specimen did not show sarcoma, but a marked "healing reaction" characterized by a proliferation of fibroblasts (fig. 21). Death was the result of pneumonia and cardiac failure. It should be noted that roentgen treatment after the first curettement did not prevent recurrence.

It will be seen that the patient in case 1 reported by Turner and Waugh was shown at autopsy to have died of pulmonary embolism. The so-called venous metastasis was likewise a small embolus in the vein, containing giant cell tissue, followed by thrombus formation as reported by Bloodgood after examination of the sections sent to this laboratory. The patient in case 2, registered by Dr. P. D. Wilson with the Bone Registry of the American College of Surgeons, showed a primary tumor of the typical giant cell variety, and a secondary change after four curettings and roentgen and radium therapy characterized by an abundance of young proliferating fibroblasts. The cause of death

on further investigation proved to be cardiac decompensation with dyspnea and edema, followed by pneumonia, in a woman, aged 70.

In brief, these two cases were both in adults over 40, occurring in the lower part of the femur and in the lower end of the radius. The first did not recur, but the second recurred repeatedly owing to incomplete primary curetting, the destruction of the bone shell and to the fact that the age of the patient was beyond the time when the healing power of the bone cell is capable of effective effort.

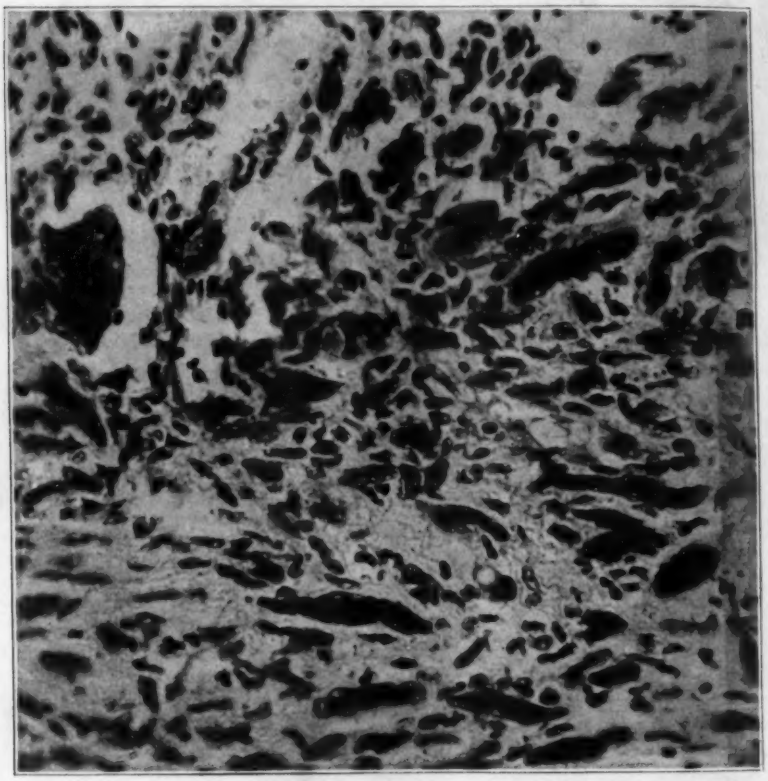


Fig. 17 (P. N. 40766, metastatic case 3 of Dr. J. L. Goforth).—High power photomicrograph showing a giant cell area bordering on osteogenic sarcoma. Sections for photomicrography forwarded to the authors through the courtesy of Dr. Goforth (specimen illustrated is from third operation).

In group 2 there are four cases, clinically similar which include those reported by Dr. Goforth,[2] Dr. Finch and Dr. Gleave, Dr. Chatterton and Dr. Flagstad, and one recorded in this laboratory by Dr. Dean Lewis.

CASE 3 (P. N. 40766, figs. 17 and 18; Dr. J. L. Goforth, case 5).—*Bone tumor; giant cell (?); tibia, upper end, left; recurrent and metastatic.*

History.—L. G., a white man, aged 34, a patient of Drs. Cooperman and Case, was admitted to the Polyclinic Hospital, Philadelphia, with the complaint of trauma to the left knee one year previously (1916) and pain and swelling of three or four months' duration.

Examination and Course.—Roentgen examination, in 1921 (before amputation), showed all the bones at the knee joint involved; bone destruction and bone formation, the bone shell of the tibia gone and joint involvement (resembled sclerosing sarcoma—Bloodgood).

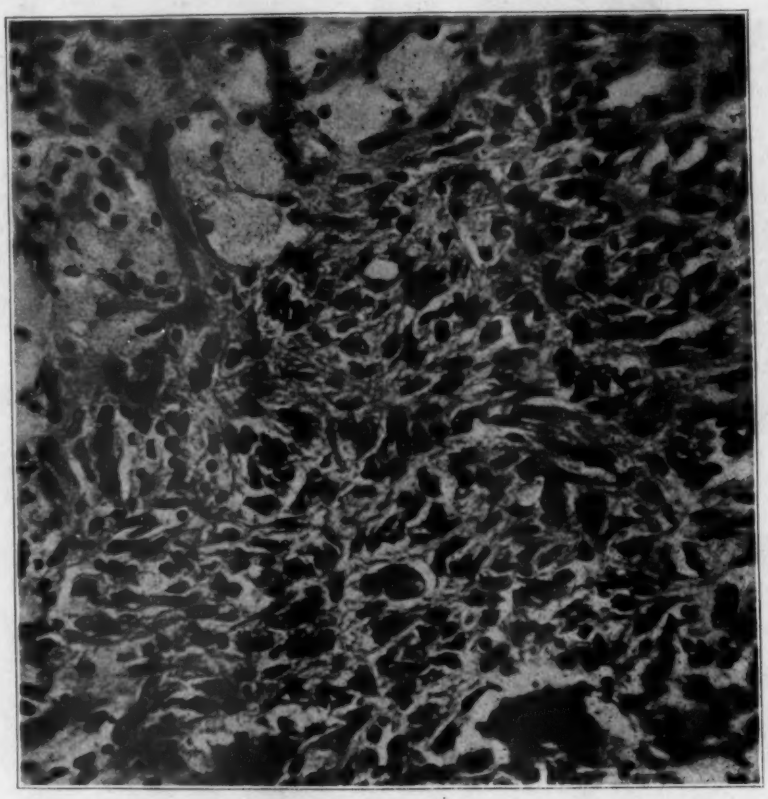


Fig. 18 (P. N. 40766, metastatic case 3 of Dr. J. L. Goforth).—Same tumor as shown in figure 17. The picture shows a cluster of foam cells occurring in osteogenic sarcoma. This tumor had perforated into the soft parts and metastasized.

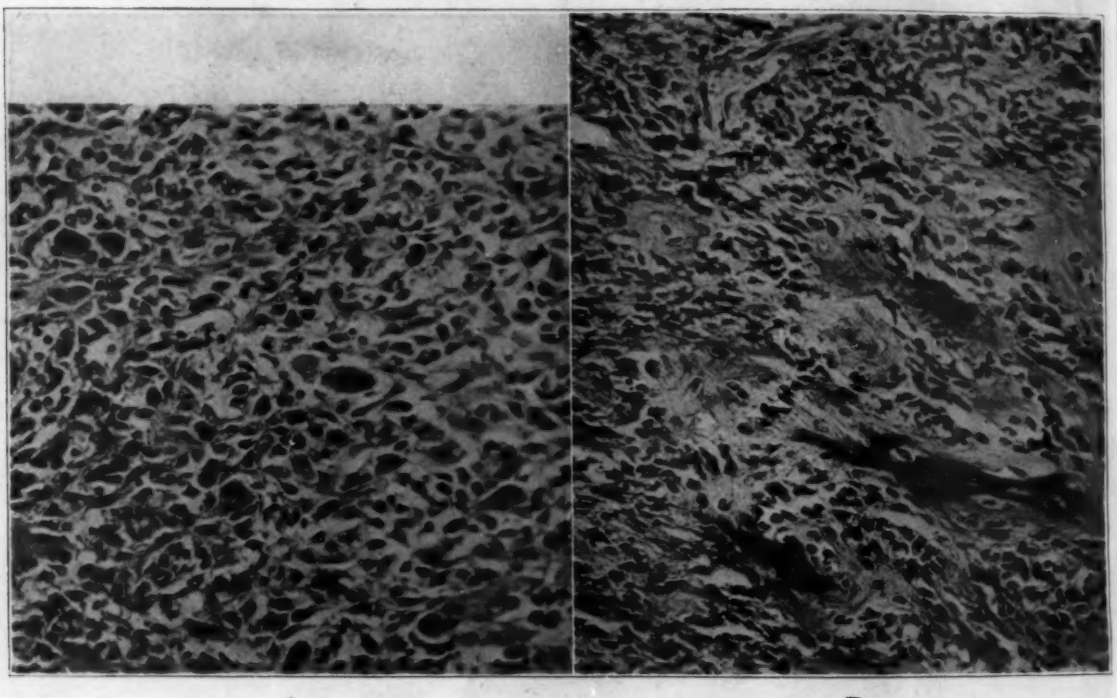
Thorough curettement was done in 1917 followed by recurrence. In 1919, a second curettement was done with no cauterization, again followed by recurrence. The patient used braces and crutches for ten months. In October, 1921, the leg was amputated above the knee.

No tissue was preserved from the first or second curettements. Tissue taken from the amputated specimen showed areas of true osteogenic sarcoma along side of areas of giant cell tissue (Bloodgood). In August, 1922, metastases to

the chest were shown by roentgen examination. Death occurred in November, 1922, six years after injury. Autopsy was not performed.

Comment.—Dr. Goforth agreed that the weak point in this case was the absence of tissue or sections from both the first and second operations. There is, therefore, no proof of the identity of the first tumor. The amputated specimen shows sarcoma. The time elapsing before amputation would permit secondary sarcoma in an unhealed lesion. There is also possibility of a slowly progressive sarcoma from the first.

CASE 4 (P. N. 40768, fig. 19; Dr. Finch and Dr. Gleave[8]).—*Bone tumor; giant cell (?); femur, lower end, right; metastatic after exploration and two pathologic fractures; recurrence in stump after amputation.*



A B

Fig. 19 (P. N. 40768, metastatic case 4 of Dr. Finch and Dr. Gleave).—*A.* Photomicrograph of a sarcomatous nodule in the lung showing small giant cells of the type frequently occurring in osteogenic sarcoma and atypical of benign giant cell tumor. Sections for photomicrography forwarded to the authors through the courtesy of Dr. Finch and Dr. Gleave. *B.* Photomicrograph of a sarcomatous nodule in the lung showing bone formation of tumor origin. This demonstrates conclusively that the metastazing lesion was osteogenic sarcoma.

History.—W. B., a white man, aged 49, a patient of Drs. Finch and Gleave, entered the Royal Infirmary, Sheffield, England, complaining of pain in the right knee in 1915; injury to "ligaments" in 1916; pathologic fracture in March, 1917, which healed after exploration and treatment; pain and swelling in 1919. In 1921

giant cell tumor was diagnosed, the original diagnosis being revised. There was recurrent pain in December, 1924, and a second pathologic fracture in January, 1925.

Examination and Course.—In January, 1925, roentgen examination showed the bone shell perforated, fracture and some new bone formation. (Gross specimen showed perforation of shell and much destruction of bone.) The first operation was performed on March 24, 1917 The site of the pathologic fracture was explored. The condition was diagnosed osteitis deformans. The fracture healed. The second fracture occurred on Jan. 18, 1925. On Jan. 21, 1925, a midthigh amputation was performed. In July, 1925, the sputum was blood stained. Recurrence in the stump occurred on Oct. 2, 1925.

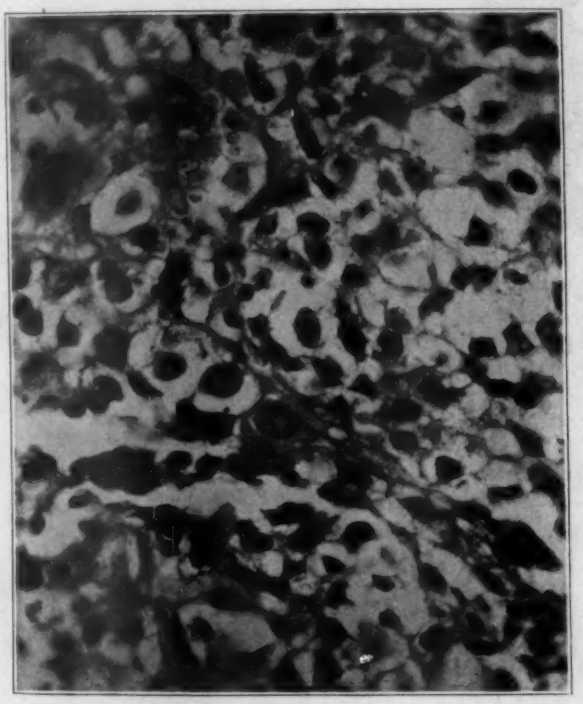


Fig. 20 (P. N. 40874, metastatic case 5 of Dr. C. C. Chatterton and Dr. A. E. Flagstad).—High power photomicrograph of a section from the tissue of the second operation. Microscopically, this tumor must be classed as a form of chondroblastic sarcoma. Material for photomicrograph was made available through the courtesy of Dr. Chatterton and Dr. Flagstad.

No microscopic report on the tissue taken from the original tumor was available. (Recurrence in stump and lung metastasis—sarcoma—Bloodgood.) On Jan. 30, 1926, eleven years after the first symptoms, the patient died. Autopsy showed metastatic nodules in the lungs.

Comment.—There is no pathologic report on the first operation in March, 1917. Sections from the amputated specimen in 1925 showed sarcoma. There is no

proof, therefore, of the nature of the primary tumor. Nearly eight years elapsed before amputation. There was ample time for a secondary growth to arise at the unhealed site.

CASE 5 (P. N. 40874, fig. 20; Dr. C. C. Chatterton and Dr. A. E. Flagstad, case 1[13]).—*Bone tumor; giant cell (?); femur, lower end, left; recurrent and metastatic.*

History.—A white women, aged 30, a patient of Drs. Chatterton and Flagstad, was first seen on Dec. 4, 1920, complaining of pain of five years' duration (since 1915), and swelling for two years (since 1918). In June, 1920, a pathologic fracture had occurred. Crutches were used thereafter. There was limitation of motion at the left knee.

Examination and Course.—In December, 1920, roentgen examination revealed an old fracture, a shell perforated and a trabeculated area of bone destruction (Chatterton and Flagstad thought bone shell intact). On Oct. 10, 1923, before amputation, there was complete destruction of the area about the old fracture with little new bone formation. On Dec. 5, 1920, curettement (partial) was performed. Cauterization was done with phenol and glycerin, and a cast was applied. Pain returned during September, 1923. On Oct. 15, 1923, the leg was amputated at the midthigh because of severe pain and fracture.

Microscopic examination of the amputated specimen of the recurrent tumor showed a condition diagnosed sarcoma (no note as to who diagnosed original sections). On Nov. 23, 1923, there was pleural effusion. Bloody fluid was withdrawn by thoracentesis. On Dec. 4, 1923, eight years after the first symptoms, the patient died.

Comment.—There is no proof of the nature of the original tumor. As the authors state: "Error in diagnosis at biopsy in 1920 must be granted because the slides and gross (specimen) have been destroyed." The length of the clinical course suggests that either a low grade sarcoma or more likely a secondary growth at the site of the unhealed primary tumor may have accounted for the death of the patient.

CASE 6 (P. N. 31890, figs. 21 and 22; JCB. N. 12425; Dr. Dean Lewis).—*Bone tumor; giant cell (?); tibia, lower end, left; recurrent and metastatic.*

History.—C. S., a white man, aged 35, patient of Dr. Dean Lewis, complained of swelling and pain in the leg of seven months' duration. The tumor recurred thirteen months after curettement. Roentgen examination showed a central, bone-destructive lesion of the epiphysis, of the lower end of the tibia. The first operation was performed by Dr. Lewis in 1908. Curettement was performed. The tumor recurred in the tibia about 2½ inches above the original site. The second operation was done by Dr. Lewis in November, 1909. Amputation was performed.

Sections from the original curetting and from amputation were lost. Dr. Lewis said that he believed the condition was typical giant cell tumor. Sections from autopsy Aug. 1, 1916, following metastases to the lungs showed osteogenic sarcoma with giant cell areas, bone lamellae and bone marrow.

The patient died in August, 1916, eight years and seven months after the first symptoms. Metastases to the lungs were demonstrated at autopsy.

Comment.—All data and specimens relating to the original tumor have been lost. Dr. Lewis states that he has never reported the case for this reason, although he believes the initial lesion to have been a giant cell tumor. Although

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13. Chatterton, C. C., and Flagstad, A. E.: J. Bone & Joint Surg. **9**:113 (Jan.) 1927.

the amputation was performed in 1909, the patient lived for seven years thereafter, suggesting the possibility of a slowly growing sarcoma.

In this group, two of these tumors were in the femur and two were in the tibia. All of these tumors recurred after initial operation, in all cases the patients were over 30 years of age at the time of amputation and in each case amputation was followed by pulmonary metastases either clini-

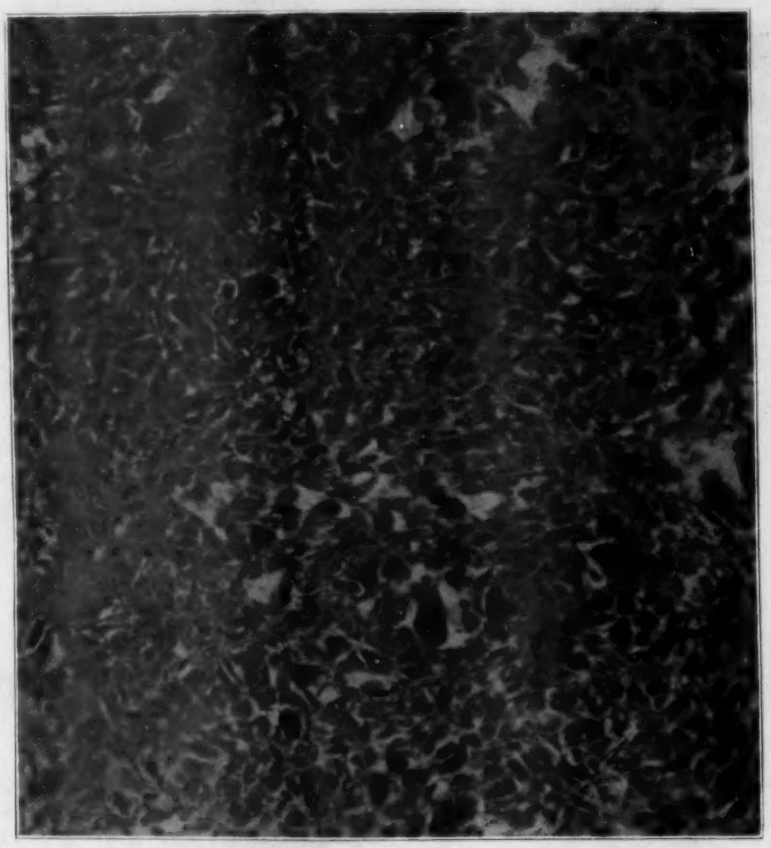

Fig. 21 (P. N. 31890, metastatic case 6 of Dr. Dean Lewis).—The photomicrograph shows a metastatic nodule in the lung with small giant cells typical of osteogenic sarcoma. The cellular stroma of the tumor is also characteristic of an early phase of osteogenic sarcoma.

cally or microscopically demonstrated. In all of these cases the duration of the interval between the first symptoms and death was over six years, and in no case was the material from the original lesion preserved; so that microscopic confirmation of the nature of the primary growth could not be carried out at the time of reporting the case. The nature of the

recurrent growth giving rise to the metastases, however, has been studied by us in each instance, and is unquestionably osteogenic sarcoma. In these four cases, therefore, we have a primary lesion of the leg, of undetermined microscopic nature, unsuccessfully treated giving rise—after an interval of years—to a metastasizing bone lesion. The long interval of time consumed by the clinical course of these growths suggests that two separate bone lesions, one superimposed on the other accounted for

Fig. 22 (P. N. 31890, metastatic case 6 of Dr. Dean Lewis).—Another portion of the same metastatic lung nodule shown in figure 21. Here the tumor has progressed to mature bone formation showing highly developed bony lamellae and actual cellular bone marrow. This highly differentiated structure is most unusual in osteogenic sarcoma, and must be attributed to the slow growth of the nodule which was excised at the autopsy table six years and nine months after the original tumor had been amputated from the leg. This sarcomatous nodule in the lung was, therefore, of approximately seven years' duration.

the manifestations observed. The important point to be emphasized is that sarcoma arose in a bone at the site of a previous lesion that had failed to heal and that had been subjected to trauma and to unsuccessful operative procedures. Failure to heal can be attributed to the age of the

patients (over 30), and to the mode of treatment instituted. The fact that sarcoma eventually arose at these sites has no bearing on the relation of the original lesion to the sarcoma, for squamous cell carcinoma has been known to occur in a draining sinus of chronic osteomyelitis for which the patient has been unsuccessfully treated, and we have observed such carcinoma in the unhealed sinus of a giant cell tumor curetted ten years previously. No one would claim that the giant cell tumor in this case underwent carcinomatous transformation. Thus in group 2, we have four cases of osteogenic sarcoma arising secondarily at the sites in bone which were the seats of unhealed previous lesions. The nature of the original lesion is not known with certainty. In one case osteitis deformans was suspected at the time of exploration. In the other cases benign giant cell tumor was suspected.

Since sections from the original lesions are not available for microscopic study, the possibility of a slowly growing sarcoma, present from the first, must be considered. In this connection it is significant that the form of osteogenic sarcoma present in these cases of recurrent lesions resembles a type of fibroblastic origin, which is usually slowly fatal and occurs generally in patients over 30, as shown by a study of over fifty cases to be reported later.

In group 3 there are two cases: one reported by Drs. Stone and Ewing, and recorded in this laboratory by Dr. T. A. Dingman.

CASE 7 (P. N. 40872, fig. 23; Dr. Martin, Dr. Coley, Dr. Stone, Dr. Ewing[7]). *—Bone tumor; giant cell (?); tibia, upper end, right; recurrent and metastatic.*

History.—J. N., a white man, aged 19, a patient at St. Luke's Hospital and Memorial Hospital, New York City, noticed swelling, tenderness and pain in February, 1919. No history of trauma was given.

Examination and Course.—On June 29, 1919, roentgen examination revealed the bone shell intact and a central area of bone destruction. The first operation was performed in February, 1919, curettement and cauterization with phenol being done. In July, 1919, the second operation was performed, and 47 millicuries of radium emanation was placed in the cavity for forty-eight hours. There was a sinus during the winter and fall of 1919. It gradually healed without infection. In April, 1920, the sinus began to discharge. On June 4, 1920, curettement was followed by osteomyelitis. On June 30, 1920, amputation was performed. Microscopic section from the original tumor was pronounced benign giant cell tumor by Drs. Bloodgood, Wolbach, Mallory and Stewart of Leeds. Drs. Wood, MacCarty and Broder diagnosed the condition a malignant growth. Tissue from the amputated stump showed sarcoma.

In January, 1921, metastasis to the lungs was shown by roentgen examination. The patient died on March 13, 1921, two years and one month after the first symptoms.

Comment.—The age of this patient and the short clinical course suggest osteogenic sarcoma of the "chondroblastic" type which frequently shows a resorptive giant cell phase. The sections sent to us resemble this type of sarcoma, as do the sections from the amputated specimen. For comparison with thirty-two other sarcomas of this type see section IV.

Case 8 (P. N. 35226, fig. 24; JCB. N. 13714; Dr. Dingman).—*Bone tumor; giant cell tumor (?); femur, left, inner condyle above epiphysis; recurrent and metastatic.*

History.—E. T., a white man, aged 16, a patient of Dr. T. A. Dingman, Paterson, N. J., struck his knee on the floor while playing basketball five weeks previously. The knee became sore and painful after a week.

Examination and Course.—Examination revealed slight swelling and definite tenderness over the mesial side at the inner condyle of the left femur. No fluid

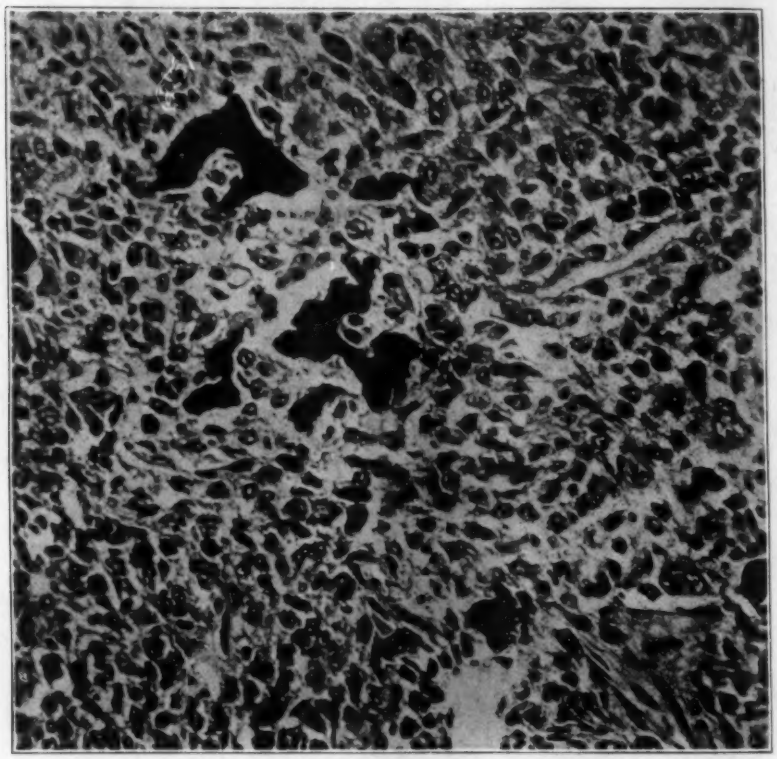

Fig. 23 (P. N. 40872, metastatic case 7 from Dr. Stone and Dr. Ewing).—Specimen from the fourth operation. The microscopic structure shown is that of the chondroblastic form of sarcoma illustrated in figures 14, 15, 20 and 24. Photographs reproduced from the article of Dr. Stone and Dr. Ewing through the courtesy of Dr. James Ewing.

was present. Roentgen examination showed an area of bone destruction beneath the cortex with overlying periosteal reaction. The first operation was performed by Dr. Dingman on April 4, 1924, curetting and cauterization with phenol being done. A second operation was performed by Dr. Dingman on April 19, 1924. The old wound was reopened and cauterization was done with electricity. On June 8, 1924, the leg was amputated by Dr. Dingman at the midthigh. There was no recurrence in the stump.

Tissue taken at the first and second operations showed typical giant cell tumor, but very cellular (diagnosed by Dr. Bloodgood, 1924). The amputated specimen showed sarcoma with altered giant cells. On August 16, bloody fluid was obtained by thoracentesis. In September, 1924, on roentgen examination, metastases were seen to the lungs and pleura. The patient died in September, six months after the injury.

Comment.—As in case 7, the clinical course and age suggest sarcoma. Restudy of the sections show "chondroblastic" sarcoma (section IV).

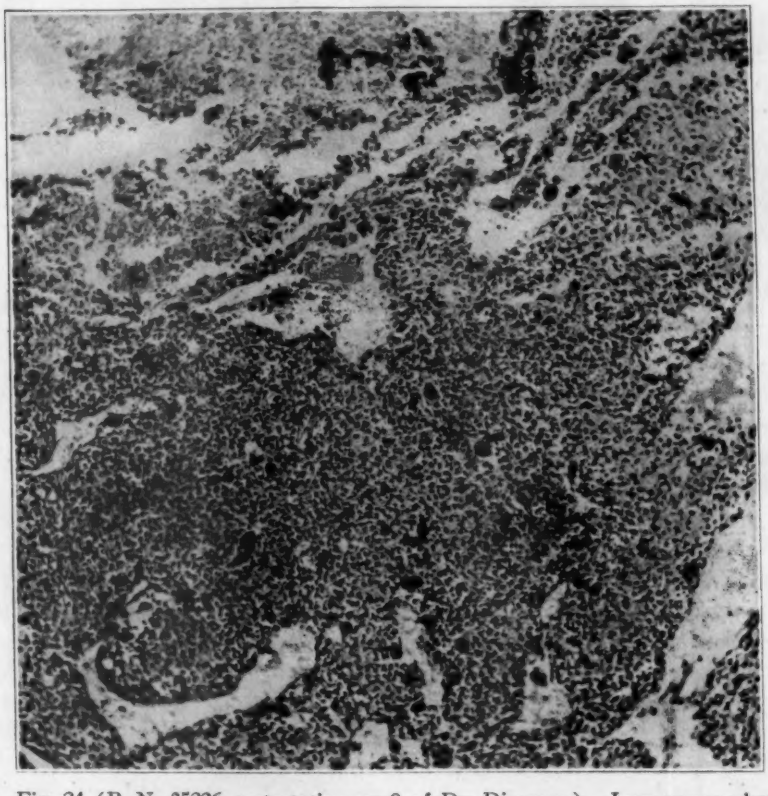

Fig. 24 (P. N. 35226, metastatic case 8 of Dr. Dingman).—Low power photomicrograph showing a chondroblastic sarcoma undergoing calcification and subsequent vascularization with giant cell invasion. Sections from this case were originally diagnosed giant cell tumor, but the patient died six months after the initial symptoms. The section illustrated is from the second operation.

Clinically, these two lesions have much in common. Both occurred about the knee joint, the upper part of the tibia and the lower part of the femur. In contrast to the other six cases, the two growths were in young men, from 16 to 19 years of age—the period of the maximum proliferative power of the bone cell—the sarcoma age. In both instances the course was relatively brief with two or more unsuccessful curettings

preceding amputation, with death by metastases in less than a year after amputation in each case. The two cases also present a similar microscopic picture. The sections show areas of round and stellate chondroblasts with a minimum amount of calcified matrix. In the vascular regions neighboring the calcified areas, giant cells are present representing the typical resorptive phase about calcified cartilage—in these instances in an abortive and malignant form. As was shown by an analysis of osteogenic sarcoma (in a forthcoming article), this type of "chondroblastic sarcoma" is frequently mistaken for other types of bone tumors, namely, round cell sarcoma of bone and giant cell tumor. In these two cases it is felt that the original lesion was a form of osteogenic sarcoma, and not giant cell tumor.

We may conclude from an analysis of these eight cases selected as avowedly metastatic from among hundreds of typically benign giant cell tumors that they are not strictly bona fide. In no case has transformation of giant cell tumor into sarcoma been proved, and in no case have typical giant cell tumor nodules been found as metastases in the lungs. In half of the cases a diagnostic error was made, either in ascribing death from other causes erroneously to metastases, or in failing to recognize the histology of the original lesion as sarcoma. In the other four cases, since material from the original lesion was not saved for confirmation of the diagnosis, there is no proof that the original tumors were typical giant cell tumors, and not a low grade malignancy from the start, nor can it be contended that the giant cell areas in the final sarcomatous growths were other than a resorptive phase in osteogenic sarcoma without histologic connection with giant cell tumor. The only plausible deduction is that in a few isolated instances an apparently benign lesion of bone, when subjected to unsuccessful treatment and to trauma, may by its failure to heal, provide a fertile site for the subsequent development of osteogenic sarcoma. The unhealed area of bone, and not the nature of the original lesion is the important factor.

IV. OSTEOGENIC SARCOMA WITH GIANT CELLS

Although osteogenic sarcoma represents the largest and perhaps the most complex group of tumors of the bone, and cannot be dealt with adequately here, still for the purpose of clarifying some of the conclusions set forth thus far, we shall anticipate briefly certain of the results of a study of these lesions to be published later, particularly those pertaining to osteogenic sarcoma with giant cells. In spite of the "consolidating" efforts of the Bone Registry and recent publications [14] endorsed by the American College of Surgeons, we are compelled to recognize on embryologic, histologic and clinical grounds, two broad and

14. Kolodny, A.: Bone Sarcoma, Chicago, Surgical Publishing Company of Chicago, 1927.

well defined groups of osteogenic sarcoma—the chondroblastic and the fibroblastic series.

As would be expected on biologic grounds, the more primitive type of chondroblastic bone formation gives rise to a more malignant and rapidly growing form of osteogenic sarcoma, while the fibroblastic series which differentiates the osteoblast or permanent bone builder, has a longer average clinical course and a higher percentage of five year cures.

Giant cell areas are not primarily characteristic of either type of osteogenic sarcoma, but may be found in both. In the slower growing fibroblastic type of osteogenic sarcoma, particularly in those cases in which operation has been performed unsuccessfully and in which there have been recurrences, foci of necrotic bone will be present, and giant cells on a phagocytic errand will invade the tumor. More frequently the presence of many small giant cells in these tumors is to be explained by a chemotaxis of these phagocytes to the collagen proliferated by these tumors which acts as a foreign body. The abundant sarcomatous tissue with immense, plump spindle cells containing vesicular and hyperchromatic nuclei should prevent confusion in making the diagnosis.

As will be gathered from the foregoing discussion of the malignant variants, and metastatic groups, it is a chondroblastic form of osteogenic sarcoma which more often leads to confusion in microscopic diagnosis (fig. 14). Four tumors classed as either malignant variants or metastatic giant cell tumor were found erroneously labeled as giant cell in origin and were rediagnosed as a form of chondroblastic sarcoma. When we compare these four tumors with twenty-nine other cases with similar clinical and microscopic features among the sarcomas, we find such a rediagnosis amply justified.

Reviewed as a single group, these thirty-three cases present remarkably uniform features. With three exceptions all occurred within the narrow age limits of from 14 to 20. Also with three exceptions, all are in the lower extremities with a period of symptoms averaging less than six months, and an average duration of life after operation of less than eleven months. Two of the four living patients have survived currettement eight and a half years and one year, respectively. The other two are living, twelve and four months after amputation. Hence, we can say that clinically this is a most rapid and malignant form of tumor.

On roentgen examination the lesion generally shows a central area of bone destruction near an epiphysis, with an early periosteal reaction (fig. 13). Under the microscope there is seen an assortment of polyhedral and angular cells with large well defined nuclei, which are in reality chondroblasts. This is proved by scanty areas of typical cartilaginous matrix laid down in a scattered fashion, here and there undergoing calcification—an abortive attempt at producing temporary or substitution bone. When occasional areas of this abortive calcified cartilage are being vascularized and resorbed by giant cell osteoclasts,

according to the usual embryologic process for substitution bone, the giant cell tumor will be simulated. It is just such areas that lead to an erroneous diagnosis of giant cell tumor, readily corrected by examination of the chondroblastic areas with small foci of calcified and uncalcified matrix. Here the malignant phase of the tumor is the rapidly proliferating chondroblast, which rarely reaches in even an abortive form the stage of calcified cartilage. The healing or reactive phase is represented by the attempt on the part of the normal bone to resorb the calcified cartilage by osteoclastic proliferation (giant cell areas) preparatory to filling in with compact "fibroblastic" bone.[15] Unfortunately, such a healed stage is never reached, but the pathologist may see just enough of the reactive giant cell phase to diagnose the lesion incorrectly as giant cell tumor.

TABLE 4.—*Summary of Treatment in Two Hundred and Fourteen Cases of Giant Cell Tumor*

Primary amputations	30 cases
Primary resections	34 cases
Curetting only	71 cases
Repeated curetting for recurrence	16 cases
Curetting plus amputation for recurrence	5 cases
Curetting plus resection for recurrence	10 cases
Curetting plus amputation for infection	3 cases
Resection plus amputation	2 cases
Exploration only	13 cases
Operation refused	9 cases
Roentgen therapy only	5 cases
No treatment recorded	16 cases
Total number of cases	214 cases
Total curettings	105 cases
Recurrent cases	31 cases
"Metastatic" cases not included in above	8 cases

V. THE TREATMENT OF GIANT CELL TUMOR

Since the effective contributions of Bloodgood to the American literature of giant cell tumor in 1910 and 1912,[16] the progress in treatment has been steadily toward increasing conservatism. Amputation, then resection and then curettement have prevailed as the treatment of choice, and now roentgen therapy alone is being advocated by some. The 214 cases forming the basis of the present study depict this evolution in treatment, these cases recording the various forms of therapy practiced since 1896 (table 4).

15. We believe this view, that the giant cell areas in chondroblastic sarcoma are a product of normal reacting bone, nearer the truth than the supposition that they are a further stage in the malignant osteogenesis of cartilaginous bone by the sarcomatous chondroblasts. Since we can observe the death of the chondroblasts with the formation of the calcified matrix, we do not see how they could survive to initiate the giant cell phase, as a further malignant product. The fact that giant cells are more numerous at the tumor margin at the site of normal reactive bone also supports this view.

16. Bloodgood (footnotes 4 and 11).

Primary Treatment.—Among the primary forms of treatment are listed amputation, resection, curettement, exploration only, roentgen therapy only and no treatment by the physician. Of these various forms, curettement has been used most frequently, although apparent cures have resulted in all six types listed. Excluding the alleged metastatic group, and a few isolated giant cell tumors of the skull and vertebrae (dangerous because of location) mortality either from treatment or from the tumor itself has been exceedingly rare indeed—less than 1 per cent.

Amputation was the primary operation in thirty cases, and although one third of these cases were explored before amputation, and twenty had shown perforation of the bone shell prior to operation, there were no recurrences, no operative deaths and no patient died of tumor. In half of these cases the patients have remained well from ten to twenty years and over, but in spite of these uniformly good results, the sacrifice of the limb in the first instance is rarely justified. Hardly ever is the lesion so advanced that the function of the limb is beyond restoration, and even when pathologic fracture has occurred, it must be remembered that the majority of these heal with appropriate treatment. Particularly in the upper extremity the conservation of the limb or even one of its minor members is worthy of trial.

Resection was performed as the initial procedure for relief in thirty-four cases. There were no deaths from either the operation or the tumor, and if we except an excision of a tumor in the lower jaw, recorded as resection, and a similar case in the radius, there was not a single recurrence. In five cases a portion of the bony shell was destroyed before operation, in three pathologic fracture had preceded, and in three other cases, there had been previous exploration. Here again the mode of treatment was usually needlessly radical, and in five cases involving the tibia and two involving the femur, in view of the functional results, curettement followed by cauterization would have been preferable. Preliminary roentgen therapy was not resorted to in a single instance in this group, and in many, the age of the patient and the extent of preservation of the bone shell favored treatment by curettage. Resection is permissible, it would seem, in advanced cases or in cases of elderly persons with involvement of the fibula, radius or ulna, although in eleven cases in the ulna, in which the patients were treated by curettement, there was not a single recurrence.

In 105 cases primary curettement was the mode of treatment. The condition in thirty-one of these cases recurred (tables 1 and 2). One patient died of a tumor in the vertebrae, and another grew progressively worse after partial curettement of a giant cell growth in the sphenoid bone. Seven patients became secondarily infected after the first or

second curettement, necessitating amputation in three instances. Several of these infections followed radium implantation into the wound, a postoperative procedure which has been proved to be ill advised in this group of tumors. Although it cannot be determined from the records in exactly how may instances, thermal or chemical cauterization followed

Fig. 25 (P. N. 26091).—Gross specimen of a giant cell tumor amputated after two unsuccessful curettings. Note the destruction of cortical bone at one side of the tumor.

curettement, it can be safely stated from this study that recurrence was more frequent in the group in which no cauterization was employed. In view of this fact, and in consideration of the fact that the patients in sixteen of the thirty-one recurrent cases were cured by a second or even third curettement, it may be stated that curettement properly per-

formed [17] in carefully selected cases is unquestionably the treatment of choice (figs. 25 and 26).

Primary roentgen treatment without operation was employed in five cases—three have been followed and are living less than five years, this mode of therapy being too recent to judge at present in regard to the ultimate result in these cases.[18] When postoperative roentgen treatments have been given in certain instances, they have not prevented recurrence and would seem to be of no particular benefit. As Bloodgood has pointed

Fig. 26.—Photomicrograph made from section taken from the specimen shown in figure 25. This giant cell tumor has not altered its typical structure despite the two previous operations.

17. The method advocated by Bloodgood consists of thorough curettage followed by cauterization with pure phenol subsequently neutralized by 95 per cent alcohol. A 50 per cent zinc chloride solution is finally applied. The electric cautery or soldering iron may be substituted for chemical cauterization.

18. In a case recently observed in a woman, aged 31, preliminary treatment had been given for six weeks for a giant cell tumor of the lower part of the radius with intact bone shell. When seen by one of us (C.F.G.), the tumor had advanced, completely destroying the shell of bone, the lesion having been uninfluenced by the roentgen treatment.

out, roentgen therapy, when compared to proper curettement, is more uncertain, often more prolonged, and does not offer the benefits of microscopic diagnosis in doubtful cases.

Nine patients refused operative treatment, and of these, seven cases have been followed: two are dead (one of hemorrhage), three are living over five years and two are well less than five years. Here there is a considerable risk of either crippling or death, and prompt treatment in view of the good results obtained in the majority of cases would have offered much to these misguided patients had they availed themselves of surgical service.

Secondary Treatment.—When curettement or excision has been followed by recurrence, the problem of the secondary treatment of giant cell tumor arises. Experience shows that little can be expected from roentgen therapy and more undesirable results may follow radium implantation into the wound. If sections or tissue are available from the original operation, they should be submitted to a competent pathologist for confirmation and check on the diagnosis of the primary growth. If not, the recurrent tumor should be reoperated on when there is an opportunity for one familiar with the microscopic appearances of this group of lesions to pass on the frozen sections at the time of operation. In any event, an attempt should be made to reevaluate the benign or malignant character of the growth. If the recurrence is benign giant cell tumor, further curettement may be tried if the lesion is in the femur or tibia, and if the age of the patient and the degree of preservation of the bone shell warrant it. In the fibula, radius, ulna or humerus, resection is advised.

Should the lesion be rediagnosed sarcoma, amputation followed by deep roentgen ray is warranted, since one five-year cure in this series was apparently achieved under such conditions. The crux of the matter, of course, lies in an accurate pathologic diagnosis.

SUMMARY

Forty-one cases of giant cell tumor showing clinical or microscopic evidence of malignant tendencies have been analyzed. In the clinical group, twenty-six cases recurring after primary curettement were studied. Recurrence in this group was found to depend not on histologic structure, but on a poor selection in the type of treatment applied in the individual case or on an incomplete operation. Advanced destruction of the bone shell, incomplete curettement, failure to use chemical or thermal cauterization or needless sacrifice of cortical bone at the operation, as well as an age over 35, were found to be factors predisposing to recurrence after curettement.

In seven cases showing a microscopic resemblance to malignancy, the histologic change was usually found to be the result and not the cause

of the recurrence, being dependent on intervening infection, necrosis or an accentuated healing reaction following irradiation. In two cases, actual sarcoma with giant cells were found to be erroneously placed in this group.

Eight cases of so-called metastatic giant cell tumors collected from the literature and from the surgical pathological laboratory of the Johns Hopkins Hospital have been reviewed and abstracted. In no case were the metastatic nodules in the lungs composed of typical giant cell tumor, and in no case was an original tumor of proved benign giant cell structure found associated with death from metastasis. In four of the cases a diagnostic error was made, either in ascribing death from other causes erroneously to metastases, or in failing to recognize the histology of the original lesion as sarcoma. In the other four cases, material from the original lesion was not saved for confirmation of the diagnosis—and therefore the possibility was pointed out, that these might have been slowly growing osteogenic sarcomas present from the first or secondary sarcomas arising at the site of an unhealed lesion in bone.

The differential microscopic diagnosis of giant cell tumor has been discussed, and a short summary of the diagnostic features of osteogenic sarcoma with giant cells included.

A review of the results of various types of treatment in over 200 cases of giant cell tumor has been presented.

THE EMPTYING OF THE GALLBLADDER FOLLOWING RESTORATION FROM ACUTE EXPERIMENTAL CHOLECYSTITIS *

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Many investigators in the field of physiology of the gallbladder maintain that the emptying mechanism of the gallbladder is a complex one associated with many interrelated factors. Others, in the light of experimental data, are inclined to emphasize the primary significance of a contractile mechanism within the wall of the gallbladder. Undoubtedly there is a fundamental factor which controls this physiologic process, and yet one which is so closely involved with other secondary factors that an exact evaluation is often difficult. Copher, Kodama and Graham (1926)[1] stated that the dilution and interchange of bile are factors influencing the mechanism by which the gallbladder empties. Other experimental observations have shown that the gallbladder may distend or recoil, reactions which are entirely independent of an active contractile mechanism.[2] It is probably true that the abundant elastic tissue within the wall of the gallbladder increases the effectiveness with which the smooth musculature operates. It has been shown, too, that the passive mechanical emptying of the gallbladder is influenced by the tonicity of the muscle bundles at the ampullar end of the common bile duct. Nevertheless, the preponderance of the experimental observations on the gallbladder, either visualized with iodized oil or by direct observation, shows that changes in the vesicle following the ingestion of a meal rich in fat are due to active intrinsic muscular contraction.[3] Graham and his colleagues maintained that although there are many experimental

* Submitted for publication, Dec. 10, 1929.

1. Copher, G. H.; Kodama, Shuishi, and Graham, E. A.: The Filling and Emptying of the Gallbladder, J. Exper. Med. **44**:65, 1926.

2. Burget, G. E.: The Regulation of the Flow of the Bile: III. The Rôle of the Gallbladder, Am. J. Physiol. **81**:422, 1927.

3. Boyden, E. A.: The Effect of Natural Foods on the Distention of the Gallbladder, With a Note on the Changes in Pattern of the Mucosa As It Passes from Distention to Collapse, Anat. Record **30**:330, 1925. Higgins, G. M., and Mann, F. C.: Observations on the Emptying of the Gallbladder, Am. J. Physiol. **78**: 339, 1926. McMaster, P. D., and Elman, Robert: On the Expulsion of the Bile by the Gallbladder and a Reciprocal Relationship with the Sphincter Activity, J. Exper. Med. **44**:173, 1926. Whitaker, L. R.: The Mechanism of the Gallbladder, Am. J. Physiol. **78**:411, 1926.

data to warrant the assertion that the contraction of an intrinsic musculature does occur, the question of primary importance is whether or not these contractions alone are sufficient to empty the vesicle. Graham had previously noted: "Shadows of diseased gallbladders were found, by cholecystography, not to change in size when the pathological changes in the wall were moderately advanced. This fact indicated that the fibromuscular layer of the wall had lost its distensibility and power of contractility. Doubtless, too, the malfunctioning of the contractile mechanism prevents normal contraction." With these clinical observations in mind, one of us (G. T. M.) undertook an experimental study of the acutely inflamed gallbladder in dogs, noting especially the response following the ingestion of the usual test meal.[4] The conclusions arrived at in his study rather definitely substantiate the hypothesis of a contractile gallbladder, in that the acutely inflamed gallbladder does not empty in the usual way following the fat meal. Histologic evidence shows that in these experimental inflammatory reactions, the entire wall of the gallbladder is invariably involved, so that the muscular layer of the vesicle has lost its power to contract. It seems evident, therefore, that the factors causing a normal gallbladder to empty following a fat meal lie within the wall of the vesicle itself and not without. For in these experimental animals, all other factors, such as intra-abdominal pressure, respiratory pressure or secretory activity of the liver, frequently credited to the mechanism active in the emptying of gallbladders, are unimpaired.

Since it was evident that the acutely inflamed gallbladder did not empty following the usual test meal, we were interested to know whether the ability to respond to the fat meal had been restored in an animal after restitution from such acute experimental cholecystitis.

TECHNIC

Acute pathologic lesions of varying degrees were produced within the walls of the gallbladders of a series of dogs following the intravenous injection of an acid solution of hypochlorite (Lorrain Smith) (eusol) identical with that employed by one of us (G. T. M.) in 1929 in his original study. Eusol is prepared by placing 12.5 Gm. of sodium hypochlorite and 12.5 Gm. of crystalline boric acid in 1 liter of distilled water. The preparation is filtered through filter paper twelve hours later and is then ready for use. Approximately 20 cc. of the solution for each kilogram of body weight was injected into the jugular vein in from one to three injections. The animals were then explored under ether anesthesia with aseptic technic, and the extent of the

4. Murphy, G. T.: The Effect of Acute Experimental Cholecystitis on the Emptying of the Gallbladder. This article will appear in a future issue of the ARCHIVES OF SURGERY.

pathologic lesions was carefully noted and recorded. Figure 1 is typical of the generalized lesion which involves a large part of the fundus of the gallbladder. The fibromuscular layer is especially involved, and the hemorrhage extends also into the elastic and subepithelial regions. The mucosa, however, is usually not involved. From four to six weeks later, under ether anesthesia, a second exploration was made. The gallbladder, which at the earlier laparotomy had shown marked cholecystitis, was now without visible lesions, and it was evident, at least grossly, that

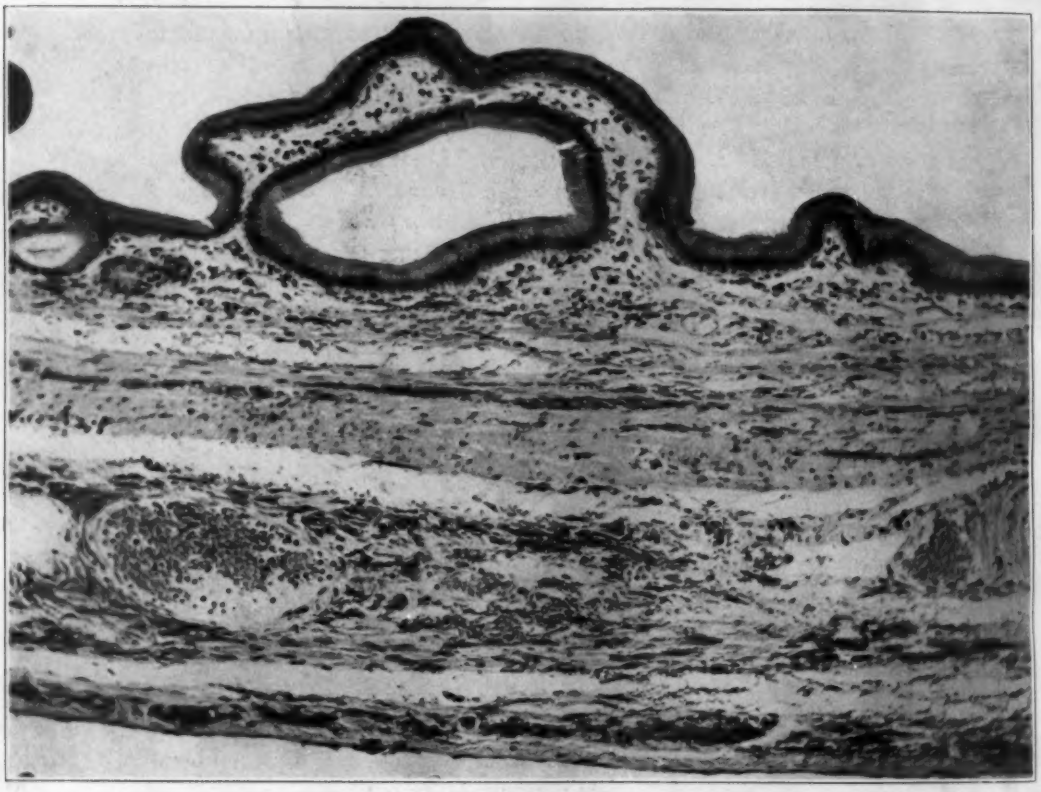

Fig. 1.—Wall of an acutely inflamed gallbladder; the vesicle did not contract following a meal of egg-yolk and cream; excessive hemorrhage throughout muscle layer is shown (× 125).

restoration had taken place. Accordingly, in order to test the emptying of the vesicle, the gallbladder was aspirated through a pursestring suture of blood vessel silk, and an equal amount of iodized oil was introduced into the viscus. From six to eight hours later the animals were given the usual amount of egg-yolk and cream, and roentgen observations were made at frequent intervals thereafter. Six dogs comprised the series of animals which forms the basis of this report.

RESULTS

Roentgen studies on the emptying of the gallbladder in these experimental animals following restitution from acute cholecystitis did not reveal appreciable differences in the reaction from the behavior of the normal gallbladder following a fat meal. All of the six animals comprising the series which had shown marked cholecystitis at the first laparotomy six weeks before now gave roentgenologic evidence of emptying within thirty minutes after eating (fig. 2). The degree of cholecystitis recognized at the first laparotomy did not appear to bear any relationship at this time to the extent to which the gallbladder emptied. In all animals, irrespective of the original lesions, the viscus discharged its contents in a normal manner, so that the emptying of

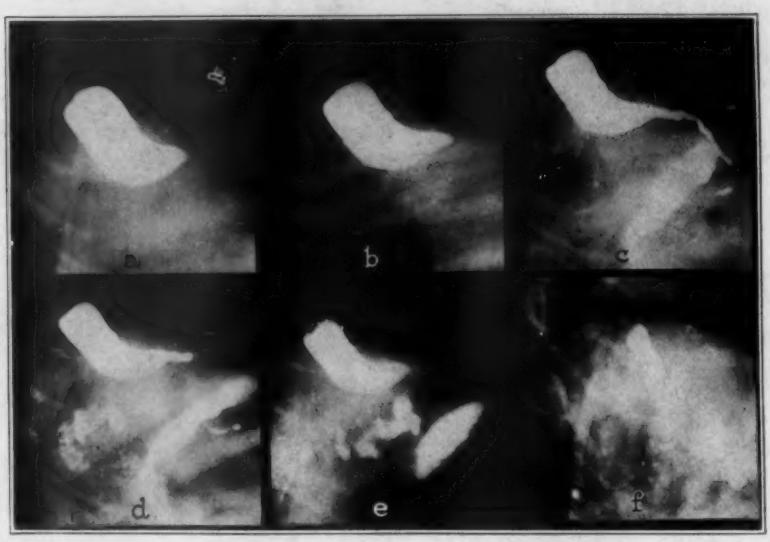

Fig. 2.—A series of cholecystograms of a gallbladder, six weeks after the development of acute experimental cholecystitis: *a*, before the feeding of egg-yolk and cream; *b*, fifteen minutes after feeding; *c*, thirty minutes after feeding; *d*, one hour after feeding; *e*, two hours after feeding, and *f*, three hours after feeding.

the gallbladder, after restoration had taken place, did not appear to be influenced by the extent of the earlier lesions. Furthermore, if we are to judge by the extent of contraction manifested by the amount of iodized oil in the duodenum and common bile duct, there appears to be a close similarity in the functional activity of these gallbladders after restoration of a normal tunic has taken place. Furthermore, there does not appear to be any significant difference in the emptying time of the gallbladder between the normal animal and these experimental dogs in which restoration had taken place following acute cholecystitis. Cholecystograms of the normal control animals following a fat meal

are generally similar to those obtained in animals following restoration. Six weeks after the development of the lesions there was no indication in any animal of this series that the function of the emptying mechanism of the gallbladder had been permanently impaired. Furthermore, histologic examination of the wall of the restored gallbladder did not show a residual lesion that could modify in any way the contraction of the

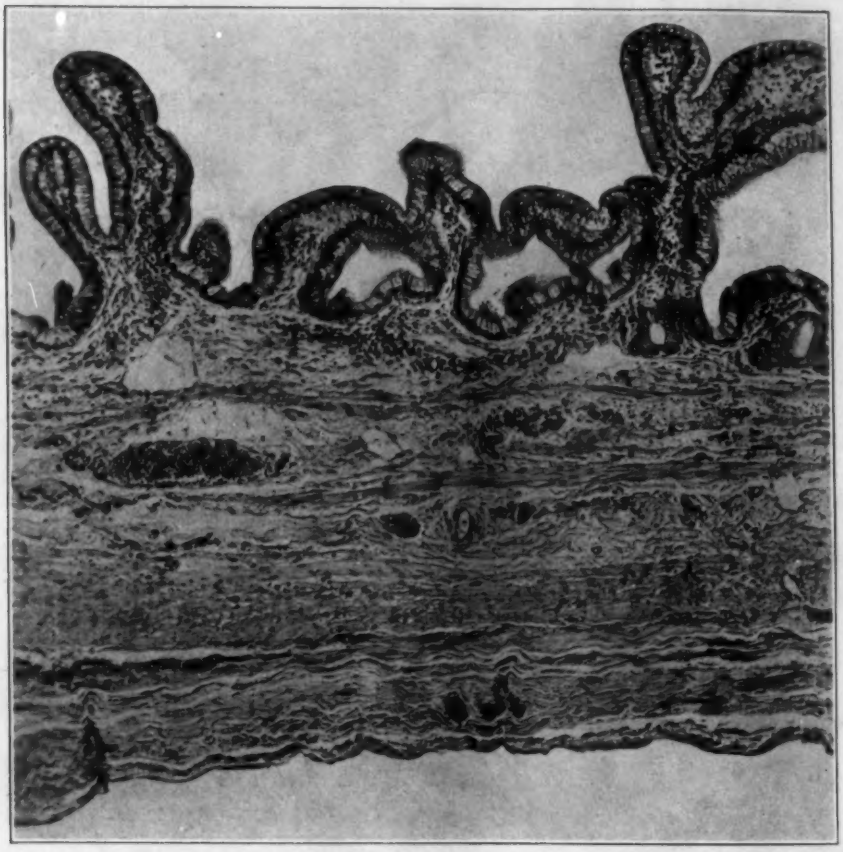

Fig. 3.—Wall of a restored gallbladder, six weeks after the development of acute cholecystitis; the gallbladder emptied following a meal of egg-yolk and cream (× 100).

intrinsic muscle layer. In some sections hemorrhagic exudates were still visible, but they were not extensive and no doubt were without effect on the discharging mechanism (fig. 3).

COMMENT AND SUMMARY

These experimental observations are of value for several reasons. In the first place, they show the rapidity with which the acutely inflamed

gallbladder may be restored to a functionally normal condition. Within from four to six weeks after the development of acute cholecystitis by the intravenous injection of eusol, the lesions had practically cleared up and, both macroscopically and microscopically, a normal condition of the gallbladder was restored. With such restoration, there was an accompanying return of functional activity, at least as far as ability to contract and thus to empty following the fat meal is concerned.

Acutely inflamed gallbladders do not empty following the usual test meal. This we believe must be due to a disturbance within the wall of the gallbladder and not to other extraneous physiologic factors. Animals with acute experimental cholecystitis are otherwise, as a rule, in good health. They ordinarily lap their meal of fat, and we have no reason to suppose that the normal digestive and assimilative faculties are in any sense disturbed. The injected solution appears to be specific for the gallbladder, for we have not identified lesions elsewhere that were induced by the injections. Accordingly, we believe that the inability of the gallbladder to empty is due to the intense inflammatory reaction which ordinarily involves the entire wall of the gallbladder, including the muscularis layer, thus inhibiting its power to contract.

When these gallbladders have been restored to a healthy condition and the inflammatory reaction has cleared up, a discharge of bile from the gallbladder invariably follows the ingestion of the fat meal. Normal, functional tissue has apparently been restored, an intact muscular layer is reestablished, and the vesicle may again respond to the factors, whether of a hormone-like nature or not, which incite the vesicle to discharge its contents.

These studies, therefore, seem to substantiate our earlier observations, and those of other workers, in the field of physiology of the gallbladder, that the primary mechanism causing the discharge of bile from the gallbladder lies within the vesicle itself. In experimental animals with acute cholecystitis, so far as we are able to determine, all other conditions are normal. Peristalsis goes on, the flow of bile remains undisturbed, and we have no reason to believe that the sphincteric mechanism at the duodenal end of the common bile duct is under unusual tonus, inhibiting the flow of bile from the gallbladder. Certainly, abdominal or respiratory pressure does not differ in these animals, and thus we believe that the structural mechanism within the wall of the gallbladder, known to be seriously impaired in these experimental animals is the factor largely responsible for the inhibitory action in cholecystitis. Accordingly, in the light of these experimental observations on both normal and abnormal gallbladders in dogs, the normal gallbladder undoubtedly empties by a contractile mechanism within the wall of the vesicle, and the diseased gallbladders do not empty because this contractile mechanism has become seriously impaired, making its usual response to the inciting stimulus impossible.

GOITROUS ENLARGEMENT OF THE THYROID GLAND DUE TO AMYLOIDOSIS*

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In generalized amyloidosis, deposits are not uncommonly found in the vessels of the thyroid as well as in other organs, but the quantity is rarely sufficient to produce enlargement of the gland or in any other way to give evidence of its presence during life. Little mention is made in the literature of amyloid goiter or localized amyloidosis of the thyroid without demonstrable deposits elsewhere. The rarity of the condition together with its interesting clinical and pathologic manifestations warrant the recording of further instances.

REPORT OF A CASE

History.—Mr. H. N., aged 54, entered St. Vincent's Hospital on the service of Dr. T. M. Joyce on March 3, 1929. The patient had noticed an enlargement of his thyroid gland for two years before admission, but no symptoms had developed until the last three months. At the time of entry, these consisted of dysphagia, dyspnea on exertion and an uncomfortable sensation of pressure in the neck. He said that he had not had a cough, fever and night sweats or any other complaint, which was surprising in view of the physical observations.

Examination.—Examination revealed a small asthenic person, with a blood pressure of 150 systolic and 90 diastolic, a temperature of 99.2 F., and a pulse rate of 84 beats per minute. He had a definitely enlarged thyroid gland, which was rather soft and somewhat irregular. The physical signs of a moderately advanced tuberculosis in both upper lobes were present and were substantiated by roentgenologic studies and examination of the sputum. His basal metabolic rate was within normal limits. The remainder of the examination gave negative results, with the exception of a secondary anemia; hemoglobin, 65 per cent; erythrocytes, 4,250,000, and leukocytes, 9,000. The Wassermann reaction was negative.

Operation and Course.—Operation was advised in spite of the active tuberculosis, because the pressure on the trachea was becoming intolerable. On March 4, 1929, a bilateral partial lobectomy was performed, and the isthmus was divided to insure relief from tracheal pressure. The gland was quite large and of most unusual appearance. It was yellowish white, of the consistency of soft butter, and was practically avascular.

The postoperative course was uneventful. The patient changed his habits as far as he was able, in order to increase his resistance to the tuberculous infection. He appeared to be getting along well in November, 1929.

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It was evident from the peculiar appearance and the absence of vascularity that we were dealing with a gland in which some unusual process was taking place, and this was borne out by the pathologic studies.

Three months following thyroidectomy, the patient was given intravenously 0.15 Gm. of Grübler's congo red dye. Colorimetric examination of the plasma withdrawn from the vein of the arm one hour after injection showed an absorption of only 22 per cent of the dye. This indicated an absence of appreciable amounts of amyloid in organs other than the thyroid gland since 60 per cent or more of the dye must disappear from the blood stream before the test can be regarded as clinically significant of amyloidosis.

Fig. 1.—Low power photomicrograph of thyroid gland which was stained with hematoxylin and eosin. Notice the great reduction in the number of alvoeli with marked distortion, and the extensive and diffuse amyloid infiltration.

Pathologic Study.—Gross Examination: The specimen, consisting of the greater part of each lateral lobe of the thyroid, weighed 248 Gm. The lobes measured 3.5 by 7 by 11 cm. and 3 by 4 by 11 cm., respectively. Externally, both were smooth, regular in outline and covered by a thin fibrous capsule. The parenchyma cut with unusual ease, and the surfaces so made were diffusely yellowish brown, soft and looked not unlike fat. Colloid was scanty, with only occasional pinpoint to pinhead sized glassy, colloid-containing areas scattered here and there throughout the gland. The trabeculae were not widened, and no nodules were observed. The gross test for amyloid, made by placing portions of the gland in compound solution of iodine followed by placing them in dilute sulphuric acid, gave a strongly positive reaction.

Microscopic Examination: Sections from various parts of the gland revealed a most striking alteration in its structure. The acini were greatly reduced in number. Those that remained, while usually fairly large and filled with colloid, were almost without exception flattened, elongated or even stellate-shaped. The colloid was vacuolated, and embedded in it were degenerating desquamated epithelial cells. In most of the acini the cells were flattened or cuboidal, but they occasionally showed slight papillary infolding. The most outstanding change, however, was the enormous amount of homogeneous hyaline-like substance which everywhere lay between and widely separated the alveoli from each other. Buried in this substance were clumps of cells which appeared to be the flattened atrophic remains of alveoli. Mixed with the homogeneous material were groups of oval or

Fig. 2.—High power microphotograph of a part of the same field shown in figure 1. The alveoli are compressed and irregular due to the abundant amyloid substance laid down between and around them. Note also the flattened atrophic acinar epithelium.

rounded vacuolar spaces having the histologic structure of fat cells. In a number of sections there were small areas of active fibroblastic proliferation, lymphoid cell collections, and what seemed to be either degenerating remnants of acinar cells or pseudo-giant cells. Such foci occurring in tissue from a tuberculous subject suggested the possibility of tuberculosis, but the absence of epithelioid cells and caseation necrosis together with the well recognized fact that closely grouped degenerating alveolar cells may resemble giant cells made this unlikely. In methyl-violet preparations, the hyaline-like substance stained a deep red, thereby proving the presence of an extensive amyloid infiltration. With this stain it was found that the amyloid completely filled most of the interalveolar vascular spaces and obliterated all save the larger vessels, and these too showed a moderate subendothelial amyloid infiltration.

Pathologic Diagnosis: The pathologic diagnosis was marked diffuse amyloidosis of the thyroid gland with atrophy and degeneration of the thyroid parenchyma (amyloid goiter).

COMMENT

The real or apparent rarity of amyloid goiter is shown by the paucity of reports in the literature. Prior to 1857, only fifteen instances [1] were on record. Peters [2] could find only ten authentic cases up to 1898, to which he added eleven of his own. In thirteen of the fifteen instances mentioned by Stoffel, there was a generalized amyloidosis occurring in the presence of such diseases as tuberculosis, syphilis or a malignant disease to explain the amyloid formation. Amyloid was present in other organs as well as in the thyroid gland in all of Peters' cases. The apparent rarity of amyloidosis of the thyroid gland may be due to a failure of workers to record their observations. Osgood [3] saw two cases among 400 selected autopsies in Erdheim's service. On the other hand, the case reported herein was the first encountered in approximately 3,500 operations on the thyroid gland in the clinic of Dr. T. M. Joyce.

Von Eiselsberg's [4] account of a syphilitic man who, because of a history of rapid enlargement of the thyroid gland, came to operation with the clinical diagnosis of a probable malignant condition, is of unusual interest. While removing the supposedly malignant gland, von Eiselberg noted a striking lack of bleeding although the patient's circulation was good. The ligatures about the vessels of the gland cut through, but still hemorrhage did not occur, and the man made an uneventful recovery except for symptoms that may be interpreted as parathyroid tetany. The goiter was remarkably brittle, bacon-like and pale yellowish. Sections stained with gentian violet gave a definite amyloid reaction. The acini were sparse, with an abundance of amyloid between them. The blood vessels, which could be found only after long search, contained no blood and showed "colloid" degeneration of their walls. The obliteration of the vascular apparatus adequately explained the lack of bleeding encountered during the operation. Von Eiselsberg could find no other instances of amyloidosis which had produced compression of the trachea. Stoffel's patient with coexistent carcinoma and amyloidosis of the thyroid gland experienced respiratory difficulty from pressure stenosis of the trachea. Stoffel stated that most of the amyloid lay in the interstitial tissue and that little was present in the blood vessel walls.

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1. Stoffel, Edda: Lokales Amyloid der Schilddrüse, Virchows Arch. f. path. Anat. **201**:245, 1910.
2. Peters, W.: Ueber einem Amyloid-Tumor mit Metastasen, Inaug. Dissertation, Tübingen, 1901.
3. Osgood, E. E.: Personal communication to the author.
4. Von Eiselsberg, F.: Ueber einem Fall von Amyloid-Kropf, Arch. f. klin. Chir. **73**:649, 1904.

More recenly, Ipland [5] recorded three instances of generalized amyloidosis in tuberculous subjects showing marked infiltration of adenomas of the thyroid gland while the remainder of the gland was comparatively free. Observations of amyloid depositions in adenomas of the thyroid gland appeared to be even more rare than those of diffuse amyloidosis.

SUMMARY

1. An instance of advanced amyloidosis of the thyroid gland producing enlargement of the gland and symptoms of pressure stenosis of the trachea is reported.

2. Chronic pulmonary tuberculosis, the most common cause of amyloid formation, adequately explains its presence in this case.

3. The results of the congo red absorption test indicate that the patient did not have a widespread amyloidosis.

4. The present study confirms the observation of previous investigators that in the thyroid gland amyloid substance is deposited chiefly in the vascular interalveolar spaces.

5. Amyloidosis of the thyroid gland is seldom encountered in surgical practice. The nature of the process may be suspected or diagnosed at operation by the bacon-like or fatty appearance of the gland and distinguished from a malignant process by the almost complete lack of hemorrhage during the course of the operation.

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5. Ipland, H.: Ueber Amyloid in Adenomen der Schilddrüse, Frankfurt. Ztschr. f. Path. **16**:441, 1915.

TREATMENT OF BRONCHIECTASIS—MULTIPLE STAGE LOBECTOMY

REPORT OF TWO CASES *

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The extensive use of iodized oil, according to the method introduced by Sicard and Forestier,[1] in the roentgenographic investigation of chronic pulmonary suppurations has shown an unsuspected frequency of bronchiectasis. It has brought about a separation of this disease from tuberculosis, chronic empyema with bronchial fistula, chronic bronchitis and even from some forms of asthma; but, on the other hand, it has also shown how often these conditions are associated with bronchial dilatations.

The most important contribution of this method of investigation has been that it has permitted tracing the disease from its earliest forms, when clinical symptoms and simple roentgenograms give no information whatever, and has established the fact of the great frequency of the disease in childhood following measles, scarlet fever and especially chronic inflammation of the paranasal sinuses. Sauerbruch [2] has even maintained that a great number of bronchiectases are due to congenital cystic dilatations of the bronchial tree.

It has thus come to be recognized that bronchiectasis is a common pulmonary disease. Hedblom [3] considered it as frequent as tuberculosis; Hamilton [4] stated that from 25 to 50 per cent of the patients

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1. Sicard, J. A., and Forestier, J.: Methode générale d'exploration radiologique par l'huile lodec (lipiodol), Bull. et mém Soc. méd. d. hôp. de Paris **46**:463, 1922; exploration radiologique par l'huile lodec, Presse méd. **44**:493 (June) 1923; Diagnostie et thérapeutique par le lipiodol, Paris, Masson & Cie, 1928 (in this volume a complete bibliography is given).

2. Sauerbruch, F.: Die chirurgische Behandlung der Bronchiektasien, Wien. klin. Wchnschr. **40**:543 (April 21) 1927.

3. Hedblom, C. A., and Head, J. R.: The Diagnosis and Treatment of Bronchiectasis, J. A. M. A. **89**:1384 (Oct. 22) 1927.

4. Hamilton, W. F.: Nontuberculous Pulmonary Disease, Arch. Surg. **14**:218 (Jan.) 1927.

sent to sanatoriums for tuberculosis have bronchiectasis, and Ochsner [5] found that 95 per cent of patients with chronic bronchitis with persistent cough show bronchial dilatation in roentgenograms taken following the injection of iodized oil.

Twenty per cent of all cases of chronic tuberculosis (Landis) and 10 per cent of cases of tumor of the bronchi or lungs, foreign bodies (Jackson [6]) or extrinsic compressions of the bronchi are complicated by bronchiectasis. This shows not only the great frequency of the disease, but also the variability of its clinical forms. As Brunn and Faulkner [7] stated, the term "bronchiectasis" must no more bring to mind the picture "of a hopeless patient with pasty septic look, harassing cough, clubbed fingers and copious foul expectoration and one whose obnoxious breath practically ostracizes him from human association." Bronchiectasis "is a very chronic disease, beginning frequently in early childhood, with symptoms of only moderate severity, extending over several years and perhaps never reaching the ultimate stages classically ascribed to it."

CLINICAL FORMS OF BRONCHIECTASIS

From the foregoing consideration it is obvious that the treatment of bronchiectasis may be a variable proposition because of the wide variety in the evolutional phases and clinical forms of the disease. It is therefore indispensable for a clearer conception of the treatment to distinguish in bronchiectasis a number of clinical varieties, as follows:

1. Bronchitic form (Ochsner [5]) in which none of the classic symptoms of bronchiectasis is present; the bronchial lesions are slight and the parenchyma of the lung is healthy. Only roentgenograms taken following the injection of iodized oil reveal the disease.

2. Early uncomplicated bronchiectasis (Hedblom [8]) in which bronchial lesions are definitely present, but are still limited to the bronchi. No pneumonitis is found in plain roentgenograms. In the roentgenograms of the bronchi there are seen cylindric or saccular dilations of the bronchi; clubbing of the fingers is present, but there is no foul sputum, or fever or loss of weight. The lesion is generally unilateral or at least more accentuated in one lung and more particularly in one lobe.

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5. Ochsner, Alton: An Unappreciated Cause of Chronic Bronchitis, J. A. M. A. **93**:188 (July 20) 1929.

6. Jackson, C.: Chronic Nonspecific Infections of the Lungs—Their Bronchoscopic and Esophageal Phases, J. A. M. A. **87**:729 (Sept. 4) 1926.

7. Brunn, H., and Faulkner, W. B., Jr.: Bronchiectasis, Am. Rev. Tuberc. **19**:191, 1921.

8. Hedblom, C. A.: Uncomplicated Unilateral Bronchiectasis: Late Results of Extrapleural Thoracoplasty, Arch. Surg. **14**:389 (Jan.) 1927.

3. Complicated bronchiectasis, with more or less advanced pneumonitis or even small multiple bronchiectatic abscesses, corresponding to the classic form of bronchiectasis (foul sputum, persistent cough, a more or less septic appearance, intermittent fever, loss of weight and markedly clubbed fingers are present).

4. Bronchiectatic abscesses, found unilobar, unilateral or diffuse, according to the distribution of the disease.

Besides these forms, which depend on the pathology of the disease, one must distinguish clinical forms according to the age of the patient and according to the evolution of the lesions.

Guibal,[9] in an excellent monograph on the subject, described as found in the young, besides the congenital forms already spoken of, other clinical types:

1. Acute bronchiectasis, which may appear in the course of whooping cough or measles and disappear without leaving any sequelae.

2. Latent bronchiectasis, chronic in its evolution, and only revealed by acute exacerbations.

3. Chronic bronchiectasis, which should be likened to the chronic form of adults, and which responds to surgical treatment.

In the adult, two forms are observed:

1. Latent bronchiectasis with acute episodes, which is compatible for a long time with good general health.

2. The chronic form.

Guibal raised an important question when he asked whether there are an acute and a subacute bronchiectasis. Oftentimes, cases have been reported in which, after an acute pulmonary disease, pneumonia or bronchopneumonia, abundant expectoration and signs of small cavitation, verified by operation, have developed (Kammerer,[10] Fränkel and Körte,[11] Delbet[12] and others). These lesions generally heal rapidly after pneumonotomy or collapse therapy (Roux-Berger, Guibal). Aschner[13] believed, and Guibal concurred in the opinion, that in these cases there is a "suppurative pneumonitis" with small abscesses developed in the parenchyma of the lung and not real bronchiectatic lesions. There is

9. Guibal, M. L.: Sur le traitment chirurgicale de la dilatation bronchique chronique; quatre observations personnelles, Paris, Masson & Cie, 1924; Bull. et mém. Soc. nat. de chir. **1**:312, 1924.

10. Kammerer, F.: Operation for Bronchiectasis, Ann. Surg. **49**:865, 1909.

11. Fränkel, A.; and Körte, W.: Gegenwartiger stand d. Lungenchirurgie, Verhandl. d. Berl. med. Gesellsch. **43**:25, 1912.

12. Delbet, P.: Sur les decollements pleuropulmonaires, Bull. et mém. Soc. nat. de chir. **47**:400, 1921.

13. Aschner, P. W.: The Pathology of Lung Suppuration, Ann. Surg. **1**:321, 1912.

no doubt that clinical observation shows a close relationship between pathologic conditions of the upper and lower parts of the respiratory tract. Acute coryza, sinusitis and tonsillitis are often accompanied by pulmonary signs or even the flaring up of old pulmonary lesions, although the intermediate section of the respiratory tract presents no change. The fact has been stressed by A. Miller of New York, in his teaching, that in old foci of tuberculosis evidenced by only a few dry râles an acute condition may develop under the influence of acute coryza or sinusitis, but that it will readily clear up following the healing of these inflammatory lesions of the upper part of the respiratory tract. In the same way, bronchiectasis in its early stages is greatly improved or even heals following treatment for sinusitis and tonsillitis and a sojourn in a dry, hot climate. I venture a suggestion that acute bronchiectasis might be due to acute lymphangitis of the bronchopulmonary and intrapulmonary lymphatic system, lymph nodes and lymph cells aggregates. Both, as is known, are located in the angles of division of the extrapulmonary and intrapulmonary bronchial tree, down to the divisions of the respiratory bronchioles and alveolar ductules. As Lerche [14] pointed out, it seems probable that their enlargement might, by a compression of the respiratory tubes, produce narrowing of their diameter and impairment of their free drainage. Incomplete bronchial obstruction and bronchial stasis would lead to signs of acute bronchiectasis, which would subside with clearing up of the initial infection and the subsequent decrease in size of the lymph nodes. It is easily understood how repeated infections of the upper part of the respiratory tract may lead to chronic adenopathy, and furthermore to a spreading of the infection from the lymphatics to the musculo-elastic element of the bronchioles, thus leading to their permanant enlargement and chronic inflammatory changes of the surrounding parenchyma. This hypothesis on which experimental investigation is now actually being carried on could give the key to the progressive nature of bronchiectasis and to its different clinical forms.

OUTLINE OF TREATMENT

The distinctions in form that have been mentioned are certainly schematic, for bronchiectasis is a progressive disease which, if left alone, tends gradually to pass from one form to the other in the great majority of cases.

It is not the aim of this paper to discuss the general treatment of bronchiectasis. I shall remark only that in the bronchitic form a careful examination and treatment of the paranasal sinuses associated with

14. Lerche, W.: Infections of the Lymphnodes of the Bronchial Tree, Arch. Surg. **16**:338 (Jan.) 1928.

hygienic measures, a hot dry climate and postural and bronchoscopic drainage, will in a number of cases check the progress of the disease.

In the second form, the early uncomplicated bronchiectasis, besides these measures, a therapeutic compression of the lung should be considered; the parenchyma of the lung is still compressible and collapsible. Pneumothorax, phrenicectomy or even thoracoplasty associated with postural and bronchoscopic drainage of the bronchi and antispirochetal treatment, when necessary, have given many satisfactory results (Hedblom [8]). It is obvious that these suggestions apply especially to cases of unilateral bronchiectasis. I do not say exclusively, because it has been shown that in cases of bilateral bronchiectasis in which there is a clearcut predominance on one side, the less affected side is greatly improved by treatment of the more affected side (see case 1).

In the third, or advanced, form of bronchiectasis with pneumonitis and multiple bronchiectatic abscesses, if the general condition of the patient allows, there is but one curative treatment, and this is the surgical exeresis of the diseased portion of the lung by lobectomy (Sauerbruch,[2] Lilienthal,[15] Robinson,[16] Brunn [17] and others), cautery pneumectomy (Graham [18]) or exteriorization and ligation of the involved parenchyma of the lung. (Zaaijer,[19] Whittemore [20] and others).

I wish to emphasize the point that bronchiectasis is a chronic and slowly progressive disease and is amenable to progressive treatment. Moreover, clinical and experimental work has convinced me that the treatment in stages as outlined, should be applied as well to advanced cases of bronchiectasis, thus preparing the ground for the terminal stage, or surgical exeresis of the diseased lung. I am convinced that by this progressive treatment not only will indications of lobectomy become less frequent, but, what is more, the present prohibitive mortality following this operation will be markedly decreased. One should keep in mind that in the progressive forms procrastination is perhaps a more

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15. Lilienthal, H.: Pulmonary Abscesses and Bronchiectasis, Ann. Surg. **59**:855, 1914; Resection of the Lung for Suppurative Infections with a Report Based on Thirty-One Operative Cases, Ann. Surg. **75**:257, 1922.

16. Robinson, S.: The Surgery of Bronchiectasis Including a Report of Five Complete Restorations, J. Gynec. & Obst. **24**:194, 1917; The Resection of Lobes of the Lung, J. A. M. A. **69**:355 (Aug. 4) 1917.

17. Brunn, H.: Surgical Principles Underlying One Stage Lobectomy, Arch. Surg. **180**:490 (Jan.) 1929.

18. Graham, E. A.: Cautery Pneumectomy for Chronic Suppuration of the Lung: A Report of Twenty Cases, Arch. Surg. **10**:392 (Jan.) 1925.

19. Zaaijer, J. H.: Zur Therapie der Bronchiektasien, Deutsche Ztschr. f. Chir. **200**;17, 1927; Surgery of the Oesophagus and Lungs, Lancet **1**:909, 1929.

20. Whittemore, W.: The Treatment of Chronic Suppurative Bronchiectasis, Ann. Surg. **86**:219, 1927.

dangerous procedure than radical surgery; that, if one is obliged to operate, this is better done while the general condition of the patient is still good, while the myocardium, the liver and the kidneys are still in good condition, and before there develop too many pleuropulmonary adhesions which may offer insurmountable technical difficulties for operation. If I am tempted to advise greater boldness for the internist, I should urge the thoracic surgeon to conservatism. I do not mean by conservatism that one should refrain from operating. On the contrary, one should and one certainly will operate in the future much more than one does now. I mean that one must not forget that thoracic surgery is the only branch of surgery in which the mere approach to the organs concerned involves an immediate and dangerous disturbance of the functions of respiration and circulation. For this reason, one should become more acquainted through experimental and clinical investigation, with the normal and pathologic physiology of these functions, as yet so incompletely known. Moreover, one should sacrifice the brilliancy of one-stage operations for the greater safety of graded ones; above all, one should adjust one's operative procedures to the resistance of the patient, preferably doing much less each time than a little more than what the patient can withstand. In other words, I am a firm believer in graded operations, which, especially in bronchiectasis, have the great advantage of gradually improving the condition of the patient, as will be shown in the remarks to follow.

Graded Lobectomy.—By graded lobectomy is meant the technic by which the patient is purposely prepared for the exeresis of the diseased lung, by systematic use, in the order given, of pneumothorax, phrenicotomy, graded thoracoplasty and, in some cases, ligature of the corresponding branch of the pulmonary artery. Several authors have reported cases in which lobectomy was performed after thoracoplasty because the latter procedure did not cure the disease; but it has not been carried out, to my knowledge, purposely as a preliminary measure to lobectomy. Sauerbruch [21] reported six cases in which lobectomies performed after ligation of the pulmonary arterial branch did not cure the disease. None of these patients died; all had bronchial fistula, five were clinically cured and one improved. It is interesting to note that the same author [22] reported four cases of lobectomy in one stage, with four deaths. Hedblom [23] advocated graded thoracoplasty in the treat-

21. Sauerbruch, F.: Chirurgie der Brustorgane, ed. 2, Berlin, Julius Springer, 1920.

22. Sauerbruch (footnote 21, vol. 1, p. 588).

23. Hedblom, C. A.: Graded Thoracoplasty for Unilateral Bronchiectasis, Wisconsin M. J. **21**:48 (July) 1922; Graded Extrapleural Thoracoplasty in the Treatment of Diffuse Unilateral Bronchiectasis, Arch. Surg. **8**:394 (Jan.) 1924; footnotes 3 and 8. Hedblom, C. A., and Head, J. R.: Use of Lipiodol in Relation to Thoracic Surgery, Ann. Surg. **85**:194 (Feb.) 1927.

ment of bronchiectasis. In three of these cases, in which the condition was relieved but not cured, he performed a secondary lobectomy in two stages. In one definite cure followed; in the other, the patient died a week after operation, and in the third the patient died during operation while traction was being exerted on the pedicle of the lung. Krause, Heidenhain, Archibald [24] and de Quervain reported similar cases, with a successful outcome. Hedblom [3] concluded: "Primary lobectomy and cautery extirpation are not to be recommended on account of the high post-operative mortality and the frequency of residual bronchial fistula. Secondary lobectomy or graded cautery extirpation, when indicated, following thoracoplasty and phrenico-exeresis should prove relatively safe and highly effective." Zaaijer [19] is the only author who advocated as successive stages phrenicectomy, thoracoplasty, thoracotomy and liberation of the diseased lung from adhesions, followed by packing, and as the last stage, resection of the involved lobe by elastic ligation of the bronchus. He remarked that "each of this series of operations may result in a clinical cure and each prepares for the following one and renders it less dangerous."

Against the views of these authors, one finds: Sauerbruch,[2] Lilienthal,[25] Tuffier, Batzdorf, Garrè, Robinson [16] and more recently Brunn [17] (with six lobectomies followed by five postoperative recoveries), who with more or less reservation are in favor of one-stage lobectomy. Whittemore [20] used to operate in one stage, but because of the high mortality (five of six operations resulting in deaths) abandoned one-stage operation and instead of resecting the involved lobe, now exteriorizes it and fixes the pedicle to the wall after resection of three ribs and allows it to slough away. He has had four postoperative recoveries in five cases in which this operation was done.

Although a few of the authors mentioned have obtained with one-stage lobectomy encouraging results in a limited number of cases, it is certain that the total mortality of one-stage lobectomy is still about 55 per cent, as is shown in the accompanying table.

Sauerbruch [26] found in the literature to 1911, 123 reports of "pneumotomies" with a total mortality of 25 per cent; cures, 33 per cent; improvements, 6 per cent, and no improvements, 27 per cent. His personal statistics [21] to 1920 give a mortality of 44.4 per cent. This shows that there is no improvement in the results of lobectomy, and although these results are still encouraging in view of the severity of the disease according to Lilienthal, one should admit that they explain

24. Archibald, E., and Brown, A. L.: Danger of Introducing Iodized Oil into the Tracheo-Bronchial System, J. A. M. A. **88**:1310 (April 23) 1927.

25. Lilienthal, H.: Statistics in discussion of Hedblom (footnote 3, p. 1390).

26. Sauerbruch (footnote 31, vol. 1, p. 585).

the hesitation of the internist and the surgeon in advising this operation and carrying it out, particularly in cases of little advanced bronchiectasis.

If one compares with these figures the results in lobectomies performed in several stages, one finds: Sauerbruch's five cases with no deaths, Guibal's one with no death, and Coryllos' two with no deaths. If one compares the results in cautery pneumectomy, one finds: Graham's forty-five cases, with freedom from symptoms after three years in 69 per cent, improvement in 7 per cent and deaths in 24 per cent; Whittemore's six cases with one death, and Hedblom's three cases with two deaths. Considering these figures, one must concede that something is wrong with the technic of one-stage lobectomy.

It will be interesting to discuss the causes of the deaths following lobectomies and study the "pathologic physiology" of this operation, if I may use this term, and see if there is any possibility of improving the results thus far given by it.

Results of One-Stage Lobectomy in Cases of Bronchiectasis

Operators	Year	Operations	Cures	Improvements	Deaths
Meyer: Tr. Am. S. A. **32**:502, 1914; Arch Surg. **5**: 361 (June) 1923	1914	16	8	..	8
	1915	1	1	..	..
Robinson [16]	1917	7	4	..	3
Hansen: Nord. med. Ark. **1**: 1, 1917	1917	4	3	..	1
Hitzrot: Ann. Surg. **71**: 785, 1920	1920	1	1	..	..
Sauerbruch [21]	1920	3	..	..	3
Graham: Arch. Surg. **3**: 321 (Jan.) 1923	1923	3	2	..	1
Guibal [9]	1924	6	1	..	5
Whittemore [20]	1927	31	7	..	24
Lilienthal [25]	1927	3	2	..	1
Whittemore [20]	1927	6	5	..	1
Brunn [17]	1929	6	4	1	1
Mortality = 55.1 per cent		87	38	1	48

THE "PATHOLOGIC PHYSIOLOGY" OF LOBECTOMY AND THE CAUSES OF DEATH

Death during or shortly after lobectomy can be ascribed to: (1) shock, cardiac failure (mechanical or reflex) or pleural shock; (2) embolism (air or septic); (3) hemorrhage during and after operation; (4) increased intrapleural pressure during the first days following operation, by pneumothorax or intrapleural fluid; (5) septic pleurisy and (6) septic mediastinitis.

Shock.—Under the general term of shock in lobectomies, one should consider inhibitory phenomena of different nature and origin, all of which lead to the arrest of cardiac function. Most often they are purely mechanical. The heart in bronchiectasis, with putrid bronchial exudate stagnating in the bronchi, generally presents a more or less advanced toxic myocarditis. Proof of this is given by the tachycardia of the patients. When the chest is opened, especially when there are no marked pleuropulmonary adhesions (as is often the case), a collapse of

the corresponding lung occurs and with the suppression of the ventilation, suppression of the pulmonary circulation results. Thus, the back pressure into the right side of the heart increases and an extra burden is thrown on the heart. Often the heart is able to withstand this extra work, but it is impossible to determine in advance how long its resistance will last. Another factor, equally impossible to gage in advance, which increases the cardiac strain, is the mobility of the mediastinum. Meyer [27] said that 50 per cent of persons have a steady mediastinum, and one thoracic cavity can be opened without disturbing the respiratory function of the other cavity. Unfortunately, one does not know in advance who these fortunate 50 per cent are. A mobile and fluttering mediastinum, after the opening of one thoracic cavity, causes an encroachment on the ventilation and circulation of the healthy lung, which is already hampered by the position of the patient lying on the healthy side of the chest.

As Eloesser [28] remarked in his paper on preliminary artificial pneumothorax, the danger is not only in the sudden collapse of the lung. When one uses positive pressure and artificially expands the lung or, especially, if the patient coughs during operation, "sudden inflation and sudden collapse produce sudden variations in the volume of blood that is thrown into and sucked out of the heart and both are equally terrifying in their effect" on the cardiac function. This "suddenness" is a dangerous element in operations in an open chest.

Besides the mechanical effect on the heart of the variations in the size of the lungs, there is a nervous effect. Through the vagi there is an interrelation between the movements of the lungs and the cardiac function. Moreover, some inexplicable deaths with sudden arrest of the heart after even slight traction on, or manipulation of, the pulmonary pedicle, may be due to an inhibitory cardiac reflex transmitted through the vagi. Sauerbruch,[29] Hedblom (1927) [23] and Eloesser,[30] each reported one death due to such a cause.

Embolism.—Cough during operation is another cause of death often ascribed to shock. During the gasping inspiration preceding and following paroxysmal cough, the mouths of pulmonary vessels are opened, and air and infectious material are easily forced into them under great pressure. Moreover, as Eloesser rightly remarked, the paroxysms of coughing aspirate and insufflate exudate and septic material from one part of the lung to another, and may obstruct a big bronchus of the

27. Meyer, Willy: On Bronchiectasis, Tr. Am. S. A. **32**:592, 1914; Observations on Lung Suppuration and Its Treatment, Arch. Surg. **5**:361 (June) 1923.

28. Eloesser, L.: Preliminary Artificial Pneumothorax in Operations on the Open Chest, Arch. Surg. **14**:439 (Jan.) 1927.

29. Sauerbruch (footnote 21, vol. 1, p. 588).

30. Eloesser (footnote 28, p. 443).

healthy lung (as in the cases of Berry [31]) and cause immediate death by bronchial reflex or obstructive atelectasis or delayed death by infection of the healthy lung.

Embolism may be connected with the much discussed "pleural reflex" or pulmonary reflex or pleural eclampsia. Lilienthal [32] did not admit the existence of the latter, considering that in the cases reported the real cause was air embolism. Hedblom,[33] on the other hand, reported a case in which he had purposed to perform a second stage extrapleural thoracoplasty for bronchiectasis. He had just opened the old incision without touching the lung when suddenly the patient went into convulsions; the pupils dilated and the patient became intensely cyanotic, but gradually revived. I have seen two similar attacks. The first occurred during a thoracoplasty, second stage, preliminary to a proposed resection of a cancerous esophagus, which was done with the patient under spinal anesthesia. There were sudden convulsions, a comatose condition, dilated pupils and cyanosis. The patient died forty-eight hours later. At autopsy, no air or other embolism or hemorrhage was found in the brain. The second attack occurred in a young woman with an abscess of the right lower lobe. Thoracotomy and a first stage cautery pneumectomy had been performed eight days previously with the patient under infiltration anesthesia, without the slightest trouble. At the second stage, just after the packing was taken off, she had an attack of generalized convulsions, rapid pulse, slight cyanosis, dilated pupils and coma. This lasted five minutes and was followed by a second one, fifteen minutes later, of the same duration. The loss of consciousness lasted about two hours; she came out of the coma gradually and completely. She had never had any attack like this previously, nor were there any thereafter. Was this a mere coincidence? At the time, I thought of a hysterical paroxysm, but my other case and the case mentioned by Hedblom [33] made me think that here is a condition that is not yet understood. Eloesser reported a case in which a sudden arrest of the heart followed clamping of a bleeding branch of the pulmonary artery near the hilum. In that case, an extreme dilatation of the right side of the heart was found. This reminds me of what sometimes happens in experimental work in the chest of the dog. Often the heart allows brisk manipulation, such as the introduction of an instrument through the left auricle or ventricle, without any disturbance of its function. At other times, with the same kind of artificial respiration, the same anesthetic (iso-amyl-ethyl barbituric acid) and the same

31. Berry, F. B.: Massive Atelectasis Complicating Paravertebral Thoracoplasty for Pulmonary Tuberculosis, Arch. Surg. **18**:257 (Jan.) 1929.

32. Lilienthal, H., in discussion of Eloesser (footnote 28), Arch. Surg. **14**:446 (Jan.) 1927.

33. Hedblom, C. A., in discussion of Eloesser (footnote 28, p. 446).

technic, without any apparent reason, the heart goes into fibrillation and stops, with the right side of the heart extremely dilated. It would appear that any vigorous manipulation in the region of the hilum of the lung is to be carefully avoided because often this can produce inhibition of the heart.

Whatever is the significance of these phenomena, one cannot deny their existence and their severity. This is one more reason for using beforehand all possible precautions so that one may operate on a wide open chest with the lung collapsed and the patient breathing quietly. The preparatory stages conducive to an uneventful operative procedure and postoperative course will be described subsequently.

Hemorrhage, Primary or Secondary.—Even with the utmost care and the use of an electric cutting and coagulating instrumentarium, it is impossible to avoid considerable loss of blood in the one-stage operation. The shock due to hemorrhage is added to the shock due to many other causes during operation. The surgeon is obliged to hurry in order to "get out" of the thoracic cavity before alarming respiratory and circulatory symptoms occur. This question of time is of paramount importance and is well emphasized by Lilienthal.[34] "I do not believe," he said, "I have ever saved one of those patients when in any stage the duration of the operation was more than 45 minutes." He also stated that cardiac imbalance occurs in proportion to the amount of manipulation required for proper exposure and also in proportion to the time consumed.

It is obvious that by speeding up during the most important stage of the operation, the resection of the diseased lung, one is apt to neglect to perform a careful hemostasis, a meticulous dissection of the pedicle and an accurate closing of the bronchial stump. This makes a secondary hemorrhage more possible and increases the chances of a tension pneumothorax and of severe postoperative infection.

Increased Intrathoracic Pressure.—Increased intrathoracic pressure, due to a tension pneumothorax or a great amount of fluid or both during the first days following operation, and the extra work thrown on the heart because of it are other causes of the high mortality in one-stage lobectomy. It is of the greatest importance that one should be able to keep the chest closed in an airtight fashion for from four to seven days after operation in order to induce the remaining lobes of the lung operated on to expand as much as possible. This complication can be avoided to a great extent by careful closing of the bronchus in several layers (Pool and Garlock[34a]). This is possible only if the pedicle has

34. Lilienthal, H.: Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 143.

34a. Pool, E. H., and Garlock, J. H.: Treatment of Persistent Bronchial Fistula, Ann. Surg. **90**:213, 1929.

been well dissected so that one can cut through the stem bronchus and not through the lung; in this way one avoids leaving a more or less considerable part of parenchyma of the lung attached to the lobar bronchus with the possibility that the circular or transfixing ligatures may cut through or release or slide with the resultant opening of tertiary bronchi. When one realizes the tremendous pressure developed during cough as measured by its expulsive force and as is easily seen in a narcotized animal in which one tries to plug a bronchus, one readily understands how a tension pneumothorax, even when due to a leakage through a small bronchial opening, can rapidly kill the patient. On the other hand, the amount of intrapleural fluid that always develops after lobectomy and the degree of postoperative, unavoidable infection are proportionate to the amount of infected pulmonary tissue left with the stump. As Brunn well remarked, "the progress of the patient depends on how thoroughly the chest cavity is kept free from air and fluid for the next five to seven days." "Therefore," he said, "I consider the closure of the bronchus a most important step, and it is my endeavor to keep the chest as free from leakage of air as possible during convalescence." But careful closing of the bronchus requires good accessibility of the hilar region and is a time-consuming procedure. So one again comes to the conclusion that in order to make possible a careful dissection of the pedicle and a good closure of it, one needs time and visibility, a combination obtainable only in the graded operation.

MULTIPLE STAGE LOBECTOMY

After this study of the pathologic physiology of lobectomy and of the causes of the high mortality incident to it, one may discuss whether lobectomy can become a safer operation than it is now, and how this can be accomplished. I think this can be done by a graded operation in which the successive stages—pneumothorax, phrenicotomy, thoracoplasty and lobectomy—are systematically carried out.

1. *Preliminary Pneumothorax.*—Pneumothorax carried on whenever feasible, and for several weeks before operation, is in my mind the most important point in a lobectomy performed in stages. Adhesions in bronchiectasis, even in its advanced forms, are generally few. I agree with Lilienthal, who stated that unless exploratory tappings have been made or an empyema has at some time developed, one should not often find important adhesions binding the bronchiectatic lung to the chest wall. It follows that a good collapse of the lung on the diseased side is generally feasible with artificial pneumothorax. In the first of my cases, the roentgenograms clearly showed that a slight pulmonary adhesion had been easily forced by raising the intrapleural pressure to a slightly positive value.

Because of the gradual collapse of the lung of the involved side, bronchial retention and stasis are decreased in proportion to the compressibility of the altered bronchi and parenchyma of the lung. Exceptionally, a kinking of a bronchus may be produced, imprisoning the bronchial exudate; this retention can easily be taken care of, when it occurs, by bronchoscopic aspiration and drainage. As a second advantage, gradual pulmonary collapse produces a gradual decrease in the flow of blood through the collapsed lung, meanwhile allowing a compensatory increase in the flow of blood and ventilation in the other lung, as Andrews [35] showed experimentally. In this way, the heart is gradually adapted to the new conditions of respiration and circulation. Churchill [36] showed that the strain on the healthy lung is small and that the circulatory burden thrown on it is not altogether borne by increasing the ventilation, but is partly compensated for by an increase in the circulatory area of the lung chiefly through the opening of new capillaries (Wearn, Barr and German [37]). The blood content of the healthy lung is increased as the rate of flow is increased (Drinker, Churchill and Ferry [38]) without marked strain on the heart.

Thirdly, collapse of the lung has as an immediate result a slowing down of the lymphatic drainage of the collapsed lung and of the lymph flow into the blood stream (Naegeli,[39] Dolley and Wiese,[40] Gardner [41]). A decrease in fever and other toxic manifestations follows, often accompanied by a marked improvement in the general condition. Moreover, this slowing down of lymph flow has as an effect a production of fibrous tissue proportionate to the degree of lymph stasis, such stasis itself being dependent on the degree and duration of pneumothorax. As a result, the visceral and mediastinal pleura become thicker and more resistant, and the mediastinum steadier; recent adhesions of no consequence for the lobectomy, due to the always present mild infection and irritation of the pleura following pneumothorax, develop and anchor

35. Andrews, de W.: Observations on Cardiorespiratory Physiology Following Collapse of the Lung by Bronchial Ligation, Arch. Surg. **10**:506 (Jan.) 1925.

36. Churchill, E. D.: The "Strain" on the Collateral Lung in Collapse, Therapy **18**:553 (Jan.) 1929.

37. Wearn, J. T.; Barr, J. S., and German, W. T.: Proc. Soc. Exper. Biol. & Med. **24**:114 (Nov.) 1926.

38. Drinker, C. K.; Churchill, E. D., and Ferry, R. M.: Am. J. Physiol. **77**:59 (Aug.) 1926.

39. Naegeli: The Changes of the Serological Reaction of the Blood After Extrapleural Thoracoplasty (quoted in Dolley & Wiese, footnote 40), Beitr. z. klin. Chir. **90**:351, 1914.

40. Dolley, F. S., and Wiese, R. E.: Effects of a Large Closed Bilateral Pneumothorax on Thoracic Lymph Flow, Arch. Surg. **18**:542 (Jan.) 1929.

41. Gardner, L. V.: The Pathology of Artificial Pneumothorax in Pulmonary Tuberculosis, Am. Rev. Tuberc. **10**:501, 1924.

the mediastinum and thus increase its stability. Furthermore, prolonged pneumothorax decreases the secretory and absorbing capacities of the pleura.

2. *Phrenicectomy.*—Phrenicectomy, performed as a second stage, is an excellent addition to pneumothorax and a valuable aid in obtaining further collapse and immobilization of the lung, particularly because of the predilection of bronchiectasis for the lower lobes. Alexander [42] considered that the paralysis of the diaphragm acts more by immobilizing than by causing further collapse of the lung. This is shown by the marked improvement even in cases of bronchiectasis, as well as in those of tuberculosis, in which the base of the lung and the diaphragm are immobilized by strong adhesions and in which no appreciable elevation follows the operation. It is obvious that in these cases paralysis of the diaphragm acts only by further immobilization of the lung. Preliminary pneumothorax carried on for a sufficient time and followed by phrenicectomy requires that the patient accommodate himself to breathing with only one lung; it steadies the mediastinum, produces thickening of the pleura and decreases the absorption from the serosa.

3. *Thoracoplasty.*—These results are further enhanced by extrapleural graded thoracoplasty limited to the affected area and performed in as many stages as are necessary. Thoracoplasty as a preliminary stage is extremely valuable. Not only does it further increase the collapse of the lung, especially when pleuropulmonary adhesions are present and pneumothorax is not successful, but it decreases the capacity and depth of the thoracic cavity. After thoracoplasty has been performed, the fourth stage of the operation, namely, exploration of the lung and its resection, is greatly simplified; no time is spent in the resection of ribs and opening of the thoracic wall, no hemorrhage is produced, the wall has lost its rigidity and can easily be retracted and the hilar portion of the lung is accessible because the collapse of the wall has brought this region nearer to the surface. Last but not least, the remaining lobe, on expanding, can more readily fill up the reduced thoracic cavity and thus shorten the time for anatomic and physiologic recovery.

It is really impressive how lobectomy becomes a relatively easy operation after these preliminary stages, pneumothorax, phrenicectomy and thoracoplasty, especially because of the absence of disturbances of respiration and circulation. When, after these stages have been performed, the chest is opened, the patient breathes as if the chest were closed. It is astonishing, as Eloesser remarked, to see the patient breathing quietly with the thoracic wall wide open and the homolateral lung completely collapsed. A collapsed lung and quiet respiration give

42. Alexander, J., in discussion of Dolley and Wiese (footnote 40, p. 552).

plenty of room to operate and perfect visibility—a perfect combination for a quiet and accurate operation. Separation of the affected lobe from adhesions, isolation of its pedicle, clamping of vessels and careful closure of the stump after resection can all be performed with surprising ease, and ease in lobectomy makes for accuracy and speed.

Thus the principal dangers in lobectomy are eliminated or greatly palliated; namely, shock, cardiac failure, reflex inhibitory phenomena and hemorrhage. A careful dissection of the pedicle allows cutting of the bronchus and no cutting through the lung tissue; thus almost no infected pulmonary parenchyma is left in the stump. This lessens the degree of postoperative infection in the thoracic cavity, which should be closed in an air-tight manner, permits one to keep the thoracic cavity closed for several days and thus allows the remaining lobes to expand. Lastly, reduction in the size of the thoracic cavity due to the thoracoplasty makes its filling with expanded lobes more feasible; pleural sinuses tend to disappear and bronchial fistula tends to heal promptly.

By the use of the technic described, opening of the chest becomes almost no more troublesome than laparotomy. With respiratory and circulatory functions undisturbed, one is able to operate on intrathoracic organs as on intra-abdominal organs, the resection itself of the diseased lung being reduced to almost a minor operative procedure. The presence of extremely strong adhesions intimately uniting the lung to adjacent lobes, parietal pleura and diaphragm may render separation of the bronchiectatic lung impossible. Such adhesions are rare and are generally observed in bronchiectasis following empyema. These adhesions are suspected when repeated attempts at pneumothorax have been unsuccessful. In these cases, lobectomy may be impossible, and cautery pneumectomy then is the method of choice. Even in the cases in which a separation of the affected lobe has been possible, but has required prolonged manipulation, one should not consider it wise to perform lobectomy at this stage. In these cases, two procedures may be employed. The lobe may be covered completely with a large piece of rubber tissue after having been separated from the adjacent structures—lung, diaphragm and parietal pleura and the thoracic wall accurately and completely closed and air-tight tube drainage of the pleural cavity instituted. From four to ten days later, the cavity is reopened and the lobe resected, following the technic advised by Lilienthal;[34] or, after separation of the bronchiectatic lobe from the adjacent lobe, the branch of the pulmonary artery is found and ligated. The last procedure was advised by Bruns and Sauerbruch,[43] who from experimental results

43. Bruns, O., and Sauerbruch, F.: Die kunstliche Erzeugung von Lungenschrumpfung durch Unterbindung von Aesten der Pulmonarterie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:343, 1911.

concluded that it could serve as a curative procedure for bronchiectasis. It is known that ligature of a lobar pulmonary artery produces atelectatic shrinkage of this lobe with subsequent development of connective tissues and fibrotic sclerosis of the pulmonary parenchyma. Unfortunately, this sclerosis is not sufficient to produce complete collapse and closure of the dilated bronchi because of the induration of their walls. Sauerbruch [44] used this method in fourteen cases of advanced bronchiectasis, without any definite results. In six of these cases, thoracoplasty and lobectomy were later performed. Ligature of the pulmonary artery is technically easy in the inferior lobes and is an excellent preliminary measure in the cautery pneumectomy of Graham,[18] when feasible, because it eliminates the dangers of hemorrhage and air or septic embolism in this otherwise excellent method.

It is even possible that ligature of the pulmonary artery in cases of uncomplicated unilateral bronchiectasis might prove a curative method when combined with thoracoplasty.

Whittemore [20] described and successfully performed exteriorization of the affected lobe after resection of several ribs. He liberated and delivered as much of the lobe as possible out of the chest and fixed it there by suturing it to the muscles of the thoracic wall. After a variable time, the exteriorized lobe became necrotic and sloughed away. Five of six patients on whom he performed the operation were clinically cured; the sixth died. There is no doubt that this procedure has some marked advantages over lobectomy and deserves a serious trial. It is not within the scope of this paper to enter into details; it aims only to show the marked advantages of a graded lobectomy in which the successive stages are systematically performed in the order described.

There are authors who still advocate the use of the one-stage operation. Lately, Brunn,[17] in a paper read before the American Association for Thoracic Surgery, reported six cases with five cures and only one death. Although I greatly appreciate these results and the skill of the operator and I profess the greatest admiration for the pioneer work of Sauerbruch and Lilienthal, I confess that I believe that graded lobectomy is a much safer operative procedure.

The two cases reported here are offered in support of these views.

REPORT OF CASES

Two cases only are given, and these are chosen because the operations in both were performed over two years ago; hence one may judge of the late results. The other cases will be reported in a forthcoming paper. Thus far there has been no mortality during the last stage.

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44. Sauerbruch (footnote 21, vol. 2, p. 572).

The first was a case of advanced bronchiectasis in a girl of 18, with multiple abscesses, foul expectoration and extreme emaciation. Bronchial dilatation was present in both lungs but showed a marked predominance in the left lower lobe. A multiple stage lobectomy as described was performed and was followed by a complete and definite cure. The second was a case of advanced bronchiectasis, developed after pneumonia with empyema for which repeated operations had been performed. Bronchiectatic abscesses were spread over the whole right lung and were accompanied by foul sputum, fever and extreme emaciation. The same preliminary procedures, except pneumothorax, were carried out, but instead of lobectomy, cautery pneumectomy was performed. Complete clinical cure followed, with a small bronchial fistula purposely maintained and actually almost dry. This patient at the time of writing was perfectly well, although in the seventh month of pregnancy.

CASE 1.—*History.*—M. K., a white girl, aged 16, entered the medical ward of Bellevue Hospital, 2nd Division (Cornell), on March 28, 1928. Her chief complaint was persistent cough, abundant purulent, foul expectoration, loss of weight and general exhaustion. In June, 1928, she had a severe cold, diagnosed as pneumonia. After three weeks, she improved but did not get rid of the cough. In September, 1927, she began to expectorate large amounts of greenish purulent, foul sputum. Although she had postural drainage three times a day for the four months preceding admission, the amount of sputum gradually increased from 8 ounces (236 cc.) to from 15 to 20 ounces (444 to 592 cc.) daily. She lost 32 pounds (14.5 Kg.) in one year.

She had been told that she had had pneumonia in infancy. She had always been subject to colds and cough.

Physical Examination.—The patient was emaciated and looked exhausted. The skin was dry; the membranes were pale. The teeth were bad. The sinuses, examined by a member of the staff of the nose and throat department, were found healthy. The left side of the chest was diminished in size and excursion, and appeared flat in comparison with the right. The heart was normal, though slightly displaced to the left. The right lung was normal. On the left side, dulness was present posteriorly from the fifth intercostal space down to the base of the lung, where breath sounds tended to be bronchial. Vocal and whispered fremitus was increased all over the left lung, especially at the base posteriorly, and in the axillary line. Many râles were heard at the left base; less in the right lung. The abdomen appeared normal. The fingers and toes were markedly clubbed and slightly cyanotic. The temperature varied from normal to 102 F.; the pulse rate was from 80 to 120. The Wassermann reaction was negative.

The sputum amounted to from 12 to 18 ounces (355 to 532 cc.) daily. It was greenish, separated in three layers and of extremely foul odor. It showed streptococci, staphylococci, diplococci, spirochetes and large bacilli, but no tubercle bacilli, and occasional red cells.

Bronchoscopic examination showed (April 12, 1928) pus coming from the left lower lobe and to a lesser degree from the right lower lobe.

A roentgenogram showed a definite process in the left lower lobe (with mottled shadow); increased pulmonary markings in both hilar regions, especially on the left (fig. 1).

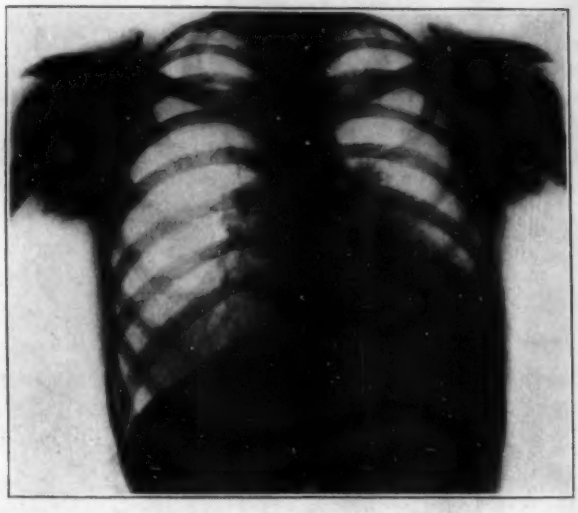

Fig. 1 (case 1).—Bronchiectasis, especially marked on the left lower lobe (April 10, 1928).

Fig. 2 (case 1).—Bronchography (lipiodol) showing bronchiectasis of left lower lobe.

Pneumothorax.—Pneumothorax was done (April 14), and the lung maintained collapsed for one month by adequate refillings. There were few pleuropulmonary adhesions (fig. 2), which were gradually forced (fig. 3) by increasing the intrapleural pressure (+6+1), so that the collapse became complete (fig. 4) within four weeks.

During this time (from April 14 to May 15, 1928), the general condition improved, expectoration diminished from 15 to from 2 to 4 ounces (from 444 to 59 to 118 cc.) daily, the foulness decreased, and the temperature returned to normal; the patient had gained 12 pounds (5.4 Kg.). She was discharged and was instructed to come regularly every week for refilling; this she neglected to do. When she came back, June 12, 1928, she was in the same condition as before pneumothorax, if not worse. The temperature oscillated between 100 and 102 F., the pulse rate around 120. There was a continuous exhausting cough with foul expectoration of

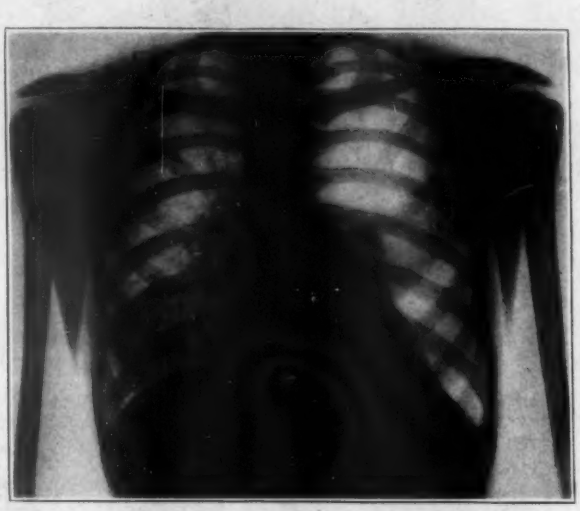

Fig. 3 (case 1).—Refilling kept on; incomplete collapse (April 23, 1929).

from 10 to 18 ounces (from 295 to 532 cc.) daily. Roentgenograms before (fig. 5) and after (fig. 6) injection of iodized oil taken the same day, showed that cylindric and saccular dilatations of the bronchi in the left lower lobe had not been influenced by the collapse of the lung. The patient was placed in the service of Dr. Alexander Miller of Bellevue Hospital for observation. A lobectomy was decided on, and the patient was transferred to the surgical ward.

Pneumothorax was started again with refillings every three days. No adhesions developed, and the lung had again collapsed completely (fig. 7). The vital capacity on June 22 was 1,900 cc. On June 25 the red cells numbered 3,100,000; the hemoglobin content was 60 per cent. The white cells numbered 12,500. A transfusion of 500 cc. of whole blood was given.

First Operation.—On June 26, 1928, a partial thoracoplasy was performed, with resection of the posterior part of the six inferior ribs, the patient being under high spinal anesthesia.

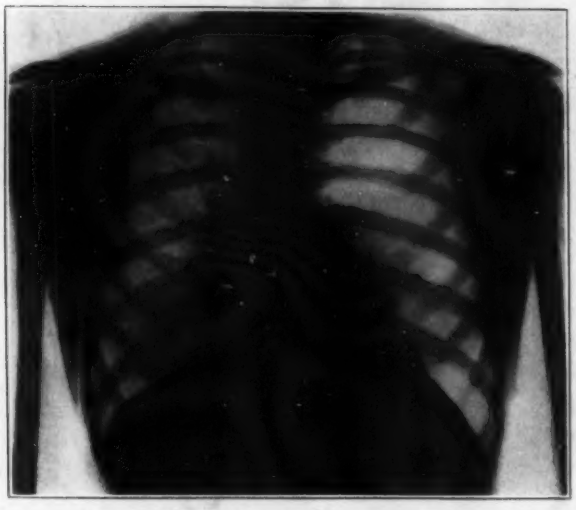

Fig. 4 (case 1).—Collapse complete. The pleuropulmonary adhesions have gradually yielded (May 4, 1928).

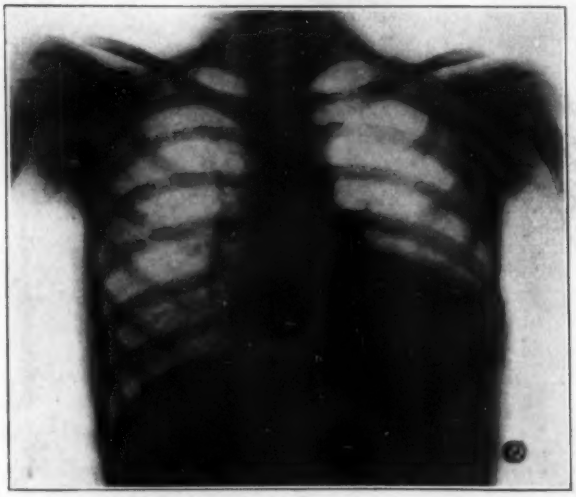

Fig. 5 (case 1).—Patient neglected to come weekly for refilling for one month and a half. The upper lobe is still collapsed, but the lower lobe is again visible (June 12, 1928).

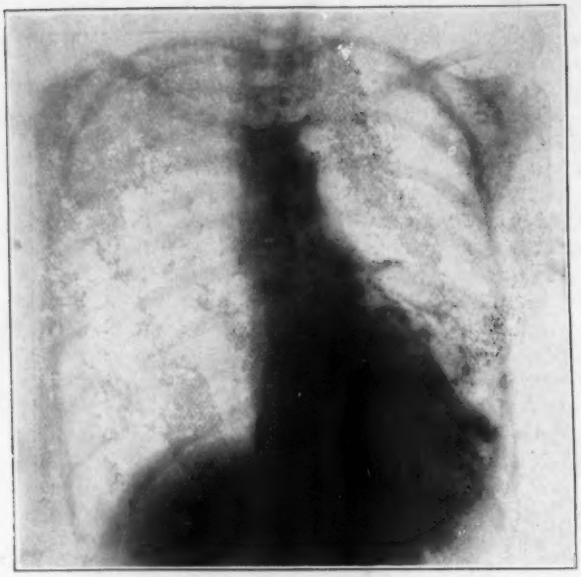

Fig. 6 (case 1).—An injection of iodized oil shows cylindric and saccular bronchial dilatation of the left lower lobe (June 12, 1928), (unsuccessful radiogram).

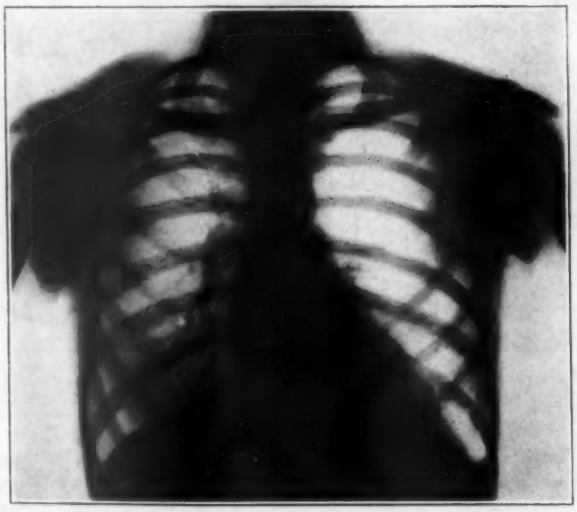

Fig. 7 (case 1).—After artificial pneumothorax, the left lung is completely collapsed, showing absence of adhesions, although the lung was permitted to expand after the previous pneumothorax. The roentgenogram was taken on June 22, 1928.

Anesthesia: Three grams of phenobarbital was given half an hour before operation. Morphine was not used. Caffeine and sodium benzoate, 7.5 grains, were given fifteen minutes before spinal anesthesia, and one ampule of ephedrine. Spinal anesthesia was obtained with 70 mg. of procaine hydrochloride. The patient sat with the head in forced flexion. The space between the fourth and fifth thoracic vertebrae was located and local anesthesia was obtained with 1 per cent procaine hydrochloride injected by means of a fine long needle inserted first horizontally then obliquely upward. The spinal fluid readily started flowing. The 70 mg. of procaine hydrochloride (Corbiere) in crystals was dissolved in 2 cc. of cerebrospinal fluid and slowly injected. No cerebrospinal fluid was allowed to flow out. The patient was left in sitting position for a few seconds and then placed flat, with the head lower than the body. Analgesia was complete from the chin to the umbilicus in about two minutes. Below the umbilicus no anesthesia of any kind (to pain, heat or cold) was present. In the arms there was complete analgesia without any motor impairment. No dyspnea or other subjective or objective respiratory disturbances were noticed, nor were there any disturbances in rhythm and rate. Blood pressure dropped within ten minutes after anesthesia from 110 systolic and 60 diastolic so as not to be recordable. The pulse was rapid and weak, but both were improved within twenty minutes after the injection. No additional ephedrine was given.

Operative Procedure: A paravertebral incision was made on the left side, 8 cm. from the line of the spinal apophyses, beginning at the fourth intercostal space, down to the eleventh and curved forward following this space, to the anterior axillary line. Incision of skin and muscle was done. A musculo-cutaneous flap was separated by blunt dissection, and the seventh, eighth, ninth, tenth, eleventh and twelfth ribs were resected from the transverse apophyses to the middle axillary line. The pleura opened accidentally above the twelfth space. Because of the already existing collapse of the lung, no disturbance whatever occurred after this pleural opening, which was immediately sutured, the intercostal blood vessels were ligated and the nerves were injected with alcohol 95 per cent, according to the technic of Hedblom. A small cigaret drain without a gage was placed under the muscles. Catgut sutures were done on the muscles, silkworm tension sutures inserted and Michell's clips placed on the skin. A dry dressing was applied. The patient was returned to bed in fair condition. The duration of the operation was forty-five minutes. At the end, slight gas-oxygen anesthesia was given, the patient feeling no pain but complaining of a "pulling up" of the ribs during their resection. Suturing required additional local anesthetic.

Postoperative Course: The postoperative course was rather stormy. The temperature went up to 105 F., the pulse to 140. The patient expectorated 18 ounces (532 cc.) of foul sputum in the evening and was greatly relieved. The temperature was normal on the third day. On the fifth day, the patient got out of bed. The cigaret tube was taken out the third day. The wound healed by primary union; the cough decreased; the sputum did not exceed from 2 to 4 ounces (59 to 118 cc.). Figure 8 shows the roentgenogram taken on the tenth postoperative day, just before the second operation.

Second Operation.—The second operation was performed on July 7, 1928. This was a second stage thoracoplasty, with resection of anterolateral portions of the same ribs with cartilaginous border, the patient being under high spinal anesthesia. Anesthesia was produced by the same procedure as had been used previously. The same results were noted and the same drop of blood pressure with rapid recovery (in sixteen minutes) followed.

Operative Procedure: A horseshoe incision was made from the fifth intercostal space, 2 cm. to the left of the sternal border, going parallel to the sternal border and curved to the median axillary line following the costal border. An incision of skin, subcutaneous tissue and muscles was made. Dissection and resection of the whole length of the cartilaginous border and of the remains of the tenth, ninth, eighth and seventh ribs which had been resected in the previous stage, was done from their angle to the median axillary line. By the same procedure the sixth rib was resected from the sternal border to the posterior axillary line. During the liberation of the costal border, the pleura was opened by an incision, 3 cm. in length, without any disturbance of the respiration. It was immediately closed by continuous suture with plain catgut. Suture of muscles by layers followed, after careful hemostasis. A rubber dam was introduced under the muscular layer. Retention sutures (silkworm) were used; the skin was sutured with plain silk. A dry dressing was applied. The patient was sent to the ward in excellent condition. The duration of the operation was fifty minutes. During the last fifteen minutes, a slight amount of gas-oxygen anesthesia was given.

Postoperative Course: The postoperative course was smoother than that after the first stage. On the seventh postoperative day there was an elevation of the temperature because of infection of the wound in the lower angle. After drainage, the temperature subsided. On July 16, the red blood cells numbered 3,200,000; the hemoglobin content was 50 per cent. A transfusion of 500 cc. of whole blood was given.

The patient was out of bed on July 21, and the wound was completely healed on August 2. The patient gained 4 pounds (1.8 Kg.); the cough and expectoration were markedly decreased, but still persisting, especially during the night. The blood, August 6, showed red cells, 4,100,000; hemoglobin, 65 per cent.

Third Operation.—On Aug. 8, 1928 (one month after the second operation), a lobectomy of the left lower lobe was done.

Pathologic Changes in Left Lower Lobe: The excised left lower lobe presented the blue-black color of an atelectatic lung, but it was elastic, not friable, crepitant, and did not sink in water; on pressure, mucopurulent froth came from the sectioned bronchi. The lobe was strongly adherent to the diaphragm and to the posterior wall. There were adhesions between this lobe and the upper lobe, which were of recent formation.

Anesthesia: High spinal anesthesia was produced with 80 mg. of procaine hydrochloride in 2 cc. of spinal fluid injected into the fifth dorsal space. Immediately after the injection and for about two minutes thereafter, there was slight respiratory distress. The patient complained she could not catch her breath. There was no acceleration or slowing of the respiration. Immediately after injection, a complete anesthesia developed from the sixth cervical vertebra down to the twelfth.

The blood pressure taken every ten minutes during anesthesia, showed a drop of 50 points in the first ten minutes after anesthesia, from 110 systolic and 65 diastolic to 60 systolic and 0 diastolic, but fifteen minutes later, it was above normal, 120 systolic and 80 diastolic and was maintained there until the end of the operation.

Operative Procedure: A long incision of the skin was made following the seventh intercostal space. Division of muscles and hemostasis followed. The ribs were represented by cartilaginous tissue, which shows how quickly the ribs are reformed. The cartilaginous tissue was cut with the knife, and the pleura opened wide from almost the sternal border to the postaxillary line. Lilienthal's retractor

was inserted, and the incision stretched. At no time was there any respiratory disturbance from the opening of the pleura. The patient continued to breathe quietly as before. The lower lobe presented the characteristics described. The lung was gently secured with Tuffer's special clamps and pulled out. The heart, the upper lobe and posteriorly the aorta and esophagus, were seen, as well as the left phrenic nerve. The adhesions to the upper lobe were separated with the finger, the pericardiopulmonary ligament was sectioned and the base of the lung slowly and laboriously liberated from the diaphragm. Two curved nephrectomy clamps were placed on each side of the bronchus, which had been dissected almost free from the pulmonary parenchyma. Traction on the bronchus was carefully avoided. On the proximal side of the clamped bronchus, silk ligatures were placed, transfixing the bronchus. Vessels were ligated separately. The clamps were removed after the section of the bronchus, and the stump of the bronchus was carefully closed with interrupted catgut sutures through the perichondrial tissues. In the center of a rubber dam 12 inches square (77.4 cm.), a small hole was made and the long threads of the ligatures passed through it, and the stump of the lobe also was forced through the opening (Lilienthal). Iodoform gauze packings were placed in contact with the stump inside of the rubber dam, the threads of the ligatures fixed on a big safety pin and left long enough to reach the thoracic wall, when slight tension was exerted on it. In the lowert part of the thoracic wall and midaxillary line a small hole was made. A rubber tube, 30 French, was introduced (air-tight) and fixed to the skin by silk string suture. Rubber dams and packings were left in the chest; the pleura was sutured with interrupted catgut sutures above them, and only the safety pin was left outside of the pleura. The muscles were sutured with interrupted catgut covering the safety pin, the position of which was marked by a small incision in the skin. Suture was on the subcutaneous tissues. No sutures were placed on the skin. A petrolatum gauze dressing was applied to the wound and covered with dry gauze. The lower drain was connected with a tube, the end of which was introduced into a bottle half filled with water in order to insure air-tight drainage. The excised lobe was sent to the laboratory. The patient was sent to the ward in fair condition. The duration of the operation was one hour and twenty minutes.

Postoperative Course: Seven and a half grains of caffeine, one ampule of digifolin and morphine, ⅙ grain, were given every six hours. On the day after the operation a transfusion of 500 cc. of whole blood was given.

The patient withstood the operation in a really remarkable way. There was little postoperative shock, and on the second postoperative day, the patient was sitting up in bed.

The first dressing was done on July 11 (third postoperative day); the sutures were cut and the thoracic cavity opened. Little, if any, infection was observed and no foul odor; 4 ounces (118.29 cc.) of dark serous fluid came out. The safety pin holding the silk sutures was located. The rubber dam was found. The iodoform gauze packing was extracted and new iodoform gauze lightly packed in; the thoracic cavity was closed with two silkworm sutures. A wet dressing sealing the opening as completely as possible was applied; on this a rubber dam was placed. The lower tube was perfectly airtight and draining fairly well.

Dressings were done every second day by changing the iodoform packing inside the rubber dam, which was left in place for twelve days. No washing or irrigation of any kind was used. The lower drain was taken out on the sixth day; on the twelfth day, the rubber dam was taken out. The silk ligatures of the pedicle were still holding. The wound led into a cavity, the size of an orange, clean,

abundantly granulating, regular, without any foul odor and almost no suppuration. Iodoform gauze was loosely packed into the cavity. The approximate capacity was 150 cc.

On the fifteenth day after operation, the stump of the pedicle sloughed away. A slight wheezing (bronchial fistula) could be heard only when the patient coughed. By the twentieth postoperative day, the cavity had greatly diminished. Slight wheezing occurred only on coughing. There was no bubbling when the cavity was filled with saline solution on ordinary respiration. The patient was out of bed on the twenty-seventh day. The capacity of the cavity was then 20 cc. The same day a roentgenogram (fig. 8) was taken. The general condition of the patient was excellent. At this time, the patient was gaining a pound (0.5 Kg.) a day.

Fig. 8 (case 1).—Seven days after graded lobectomy of the left inferior lobe. Seven inferior ribs were resected previously. The postoperative cavity is clearly seen.

On the thirtieth day, the capacity of the cavity was 10 cc. There was no bronchial fistula. The patient was discharged on the thirty-eighth day and directed to come to the ward for dressing. On the fiftieth day, the wound was completely closed. There was no bronchial fistula.

A dry cough persisted for two days following operation. Expectoration ceased completely after operation. From the third day on, there was no cough or expectoration, nor was there any at the time of writing.

The patient had gained 35 pounds (15.9 Kg.) by Dec. 15, 1928, four months after the operation. At the time of writing she was perfectly well, did not cough or expectorate, and was working as a switchboard operator.

The last roentgenogram (fig. 9) was taken in March, 1929, showed that the upper lobe was expanded and was about two thirds the size of the right lung. At that date, the patient weighed 122 pounds (55.3 Kg.), a gain of 52 pounds (23.6 Kg.) since operation; the vital capacity was 3,400 cc.

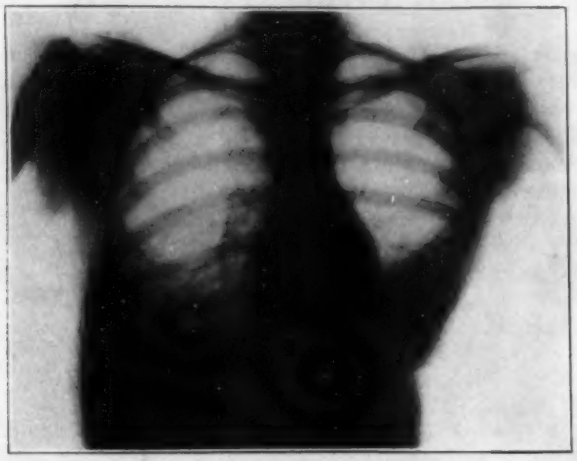

Fig. 9 (case 1).—Sixteen months after lobectomy. Left upper lobe is reexpanded (March 21, 1929).

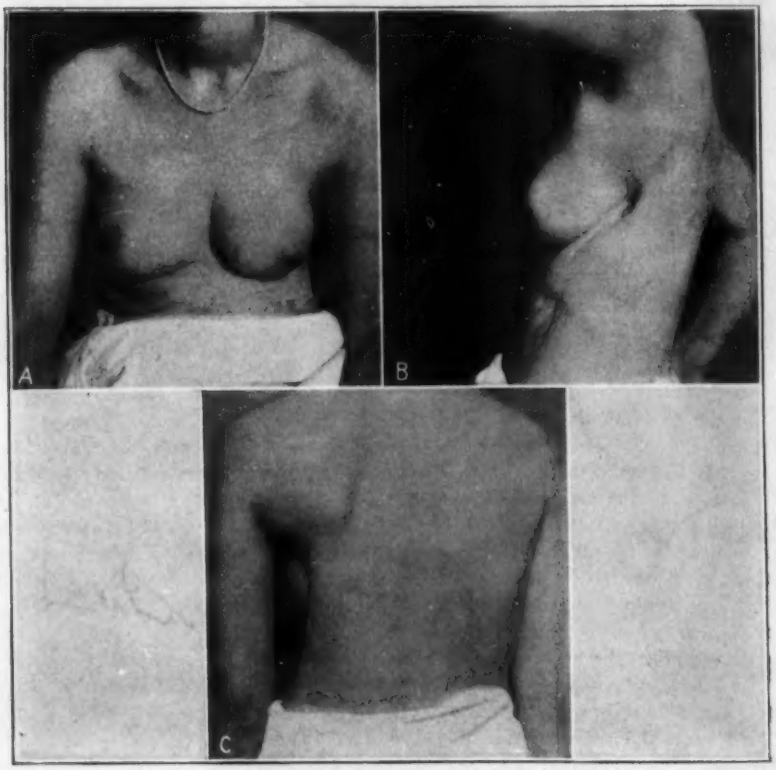

Fig. 10 (case 1).—Photographs taken eighteen months after lobectomy.

CASE 2—*History.*—V. Z., a young white woman, aged 23 was admitted to the second Surgical Division (Cornell) of Bellevue Hospital for the first time on April 6, 1926. She complained of persistent cough, foul expectoration, loss of weight and discharging sinus over the base of the chest. Two months previously she had had pneumonia complicated by empyema, for the drainage of which she had been operated on in another hospital. Irrigation with surgical solution of chlorinated soda (Dakin's solution) had also been instituted, but this was discontinued because of the formation of a bronchial fistula. She was discharged in March. For the past two weeks she had been coughing up foul sputum, which nauseated her. She had no appetite, had lost 15 pounds (6.8 Kg.) and felt "below par."

Physical Examination.—The patient was emaciated and looked chronically ill. She expectorated foul smelling sputum. The examination disclosed no abnormal conditions except in the chest, which showed limited expansion on the right side, dulness posteriorly over the right base, vesicular breath sounds, and increased fremitus. There were no signs of cavitation. A discharging sinus was found in the eighth intercostal space at the posterior axillary line. The blood count showed 14,000 white cells and a hemoglobin content of 60 per cent. The urine was normal. The sputum was negative for tubercle bacilli. The smear contained a great number of cocci and large bacilli. The blood pressure was 110 systolic and 70 diastolic. An x-ray picture showed a circumscribed infiltration in the right lower lobe, occupying the posterior part of this lobe, shown in lateral view. No definite pleural effusion was to be observed, and no fluid level. (The roentgenogram was lost.)

First Operation.—The first operation was performed on April 20, 1926 by Dr. Holder.

Pathologic Changes: The old sinus tract (partial section of the ninth rib) was explored with a Kocher clamp, which could be inserted for a depth of about 8 cm. Inspection of the abscess cavity following resection of the seventh rib in the midaxillary line, showed a cavity approximately 10 cm. in diameter, filled with foul-smelling grayish pus, much fibrin and gangrenous lung tissue. The cavity was well walled off.

Operative Procedure: Gas-oxygen-ether anesthesia was employed. The seventh rib was resected in the midaxillary line for a distance of 10 cm. The pleura was markedly thickened, and the lung was adherent to the parietal pleura. The sinus was enlarged; the contents of the abscess cavity were evacuated and a double soft rubber drain was inserted. The cavity was packed, around the drain, with 1 inch (2.5 cm.) gauze packing; a dry dressing was employed.

Postoperative Course: For four days, the patient's postoperative course was stormy. On the fifth day, the temperature became normal. On the twelfth day, the patient's cough had almost completely disappeared, and the drainage tube was removed. On the next day, the temperature rose again, and cough reappeared; the tube was reinserted. The patient was discharged on the fifteenth day, with the drainage tube in place, and requested to return to the ward for dressings. There was a little cough, and the amount of drainage was reduced.

An x-ray picture taken on Sept. 29, 1926, showed: The old resection of the seventh rib with irregular bone regeneration; a dense shadow at the base obscuring the outer half of the dome of the diaphragm and the costophrenic sinus. Diagnosis: Consolidation of the right base; no definite signs of abscess cavity. (The roentgenogram was lost).

An x-ray picture on Oct. 15, 1926 showed: in the lung, an area of consolidation with several areas of excavation at the base occupying the third, fourth and fifth interspaces; the diaphragmatic outline and the costophrenic sinus of the seventh rib partially obliterated; apparent resection of the seventh rib posteriorly. Diagnosis: Lung abscess. (The roentgenogram was lost.)

On Oct. 21, 1926 (six months after the first operation) the patient reentered the hospital. So long as the tube was kept in the sinus after the last operation, the patient was comfortable and had little cough. In September, the tube was removed and when the wound healed, she began to cough and expectorate foul sputum as before.

Second Operation.—The second operation was performed on Oct. 29, 1926, by Dr. Shepard, the house surgeon.

Pathologic Changes: The site of the rib resection at the seventh rib had been filled in with cartilage, partially calcified in places. The hiatus in the ninth rib was filled with scar tissue. There was an area of consolidation of the lung just medial and slightly posterior to the site of excision of the seventh rib.

Operative Procedure: With the patient under local anesthesia produced with 1 per cent procaine hydrochloride, an incision was made through the scar tissue in the region of the ninth rib, and the pleura at this point. The pleura was free. Just above the opening, however, were adhesions between the thoracic wall and the consolidated area of the lung which has been described. A parallel incision was then made over the region of the seventh rib, and a portion of cartilage excised. Through the opening thus made, a trench was opened into the consolidated lung by blunt dissection. This was extended to the limit to which the gloved finger could be introduced and was packed with iodoform gauze. A small rubber drain dam was inserted in the anterior angle of the lower wound, which was then closed with chromic and interrupted catgut; the latter half of the operation was performed with the patient under gas-oxygen anesthesia.

Postoperative Course: The padding inserted at operation was all removed on November 7 (nine days after operation) and a large rubber drain was inserted. A definite bronchial fistula was noted at that time. On November 9, a probe was introduced into the trench made at operation and an x-ray picture taken, which was reported on as follows: "The probe enters the abscess cavity which extends almost to the hilum. The lateral plate shows beginning sclerosis of the walls of the cavity." On November 14, the large tube was removed and a small rubber tube was inserted. The patient was referred to the nose and throat department, where it was noted by those who examined the patient that both antrums were dark; treatment was instituted. The patient was discharged markedly improved and was advised to keep the tube for several months.

On Jan. 6, 1927, the patient was admitted for the third time. She complained of weakness and swelling of the ankles about four weeks previous to admission. She had had moderate cough and foul expectoration since her discharge, although the tube had been left in place. The examination of the blood red cells 3,800,000; hemoglobin content 58 per cent. A transfusion of 500 cc. was performed, following which the hemoglobin rose to 65 per cent and the number of red cells to 4,200,000. An x-ray picture following injection of iodized oil into the sinus showed: "Multiple pulmonary abscess cavities communicating with the bronchus." The patient was discharged, January 10, on her demand, slightly improved.

On June 21, 1927, the patient came to the hospital because for seven weeks she had been coughing frequently and expectorating foul sputum (from 2 to 5 ounces [59 to 148 cc.] daily), although the drain tube was in place. She at first gained 15 pounds (6.8 Kg.), but lost it within the seven weeks.

At this point, I examined the patient for the first time. She looked emaciated and chronically ill, coughed constantly and expectorated foul sputum. The temperature was 101 F., the pulse rate 105, the respiration rate 20, the weight 78 pounds (35.4 Kg.). The x-ray picture taken following injection of iodized oil into the sinus showed multiple cavities in the posterior portion of the left side of the chest, communicating with the bronchus. The upper limits of the cavities reached the fourth intercostal space. A graded thoracoplasty was decided on. Pneumothorax was tried without success.

First Stage Thoracoplasty.—On July 5, 1927, with the patient under gas-oxygen-ether anesthesia, a paravertebral right incision and resection from the seventh to the second rib were made. The first rib was left because of the alarming condition of the patient at the end of the operation; from 3 to 6 inches (7.6 to 15.24 cm.) of each rib was resected. The postoperative course was smooth. The wound healed within ten days.

Second Stage: On July 18, 1927, with the patient under gas-oxygen-ether anesthesia, a paravertebral incision was made extending from the lower end of the incision of the previous operation downward to the eleventh rib and then outward following this rib to the anterior axillary line; the eighth, ninth, tenth and eleventh ribs were resected from their angle to the costal cartilages.

Second Postoperative Course: The patient had a severe reaction, the temperature rising to 105.5 F., with a great deal of respiratory distress. Her condition gradually improved. A hypodermoclysis employing dextrose and saline solution was done, an intravenous injection of dextrose 25 per cent was given, and on the fifth day a transfusion of 500 cc. of blood was employed. The patient responded extremely well to these measures. The wound of the thoracoplasty was infected and healed slowly by granulation. The tube was maintained in place.

The patient was discharged twenty-seven days after the second stage, markedly improved; the cough was diminished and expectoration was from 2 to 3 ounces (59 to 88 cc.) in twenty-four hours. The right side of the chest was markedly collapsed. The patient was told to come for dressings. It was explained to her that several operations would be necessary for complete cure.

Third Stage: On Oct. 30, 1927, a parasternal incision and resection of the remaining anterior segments of the second, third, fourth and fifth ribs was performed and also phrenicectomy of the right phrenic nerve.

Third Postoperative Course: A perfect collapse of the chest followed this operation. The postoperative course was smooth, the temperature oscillated between 100 and 101.5 F. for four days, then gradually returned to normal. A great amount of foul sputum was evacuated during the first five days, then the amount decreased rapidly and thirteen days later, when the patient was dischaged, she had only a slight cough and expectoration of from 1 to 2 ounces (30 to 59 cc.) of slightly foul sputum. The wounds of the thoracoplasty and of the phrenicectomy were healed.

An x-ray picture taken on Nov. 11, 1927, showed: "Right lung completely collapsed; dense fibrosis of the base." One month later, on Dec. 13, 1927, an x-ray picture was taken after injection of iodized oil through the trachea; the report was: "Base shows complete fibrosis; upper lobe is collapsed with bronchiectatic cavities."

By this time, the patient had put on 9 pounds (4.1 Kg.) since the last operation. But the cough persisted with expectoration of from 1 to 2 ounces (30 to 59 cc.) of foul sputum in twenty-four hours. Besides, although the lower lobe did not show any cavities and had undergone almost complete fibrosis, bronchiectatic cavities appeared in the upper lobes.

Fourth Stage: The patient was admitted on Dec. 18, 1927 and given a transfusion of 700 cc. of whole blood. The fourth stage of the operation was performed on Dec. 20, 1927.

Pathologic Changes: The thoracic wall was collapsed and all the ribs resected, except the first, in previous operations. The lung was collapsed, dark and adherent to the parietal pleura; the distinction of the different lobes was difficult. A number of cavities of sizes varying from a walnut to a hazelnut and smaller, were found in the pulmonary parenchyma of the three lobes, containing foul smelling fluid and gangrenous tissue. It was felt that there were still other cavities present.

Operative Procedure: With the patient under gas-oxygen-ether anesthesia, a horse-shoe incision was made, going from the anterior axillary line and the second space downward to the level of the tenth rib and then upward and backward to the third space, on the spinal border of the scapula. The chest flap, composed of skin and muscles, was reflected upward, and the pleura, completely adherent to the underlying collapsed lung, exposed. A soldering iron, heated to cherry red, was plunged into the parenchyma of the lung and the cavities mentioned, opened. Four cauterizations were made, the iron penetrating each time to a depth of from 1¼ to 2 inches (3.1 to 5 cm.). The moderate hemorrhage was easily checked by packing. A Mikulicz rubber pad was inserted and solidly packed with iodoform gauze. The flap was deflected and temporarily sutured with two sutures of silkworm gut only.

Fourth Postoperative Course: The postoperative course was remarkably smooth. The temperature did not rise above 101 F.; cough and expectoration greatly decreased.

The cauterization of the lung was repeated on January 4 and 11. In each stage, new abscesses were opened. The moderate hemorrhage was easily checked by compression. The wound was left open and packed with a large piece of rubber dam containing iodoform gauze.

After the third cauterization, the patient's condition showed a remarkable improvement. The cough and expectoration ceased completely, the wound was clean, showing a great number of bronchial orifices on its surface; gangrenous tissue was eliminated and healthy granulations were filling up the wound. The foul odor had disappeared. The dressing with the rubber pad tightly packed with iodoform gauze was kept on. The patient was discharged on Jan. 28, 1928, and instructed to come every day for dressings.

By March 1, 1928, the wound had gradually decreased in size, showing bronchial orifices in it depth, from which air was freely going in and out. The cough and expectoration had disappeared completely. There was no foul odor or taste in the mouth. There was little discharge from the wound. The patient gained 20 pounds (9 Kg.) in three months and felt fine, perfectly well and happy. A tube was inserted in the orifice to avoid possible closing. A roentgenogram (fig. 11) showed the lower lobes fibrotic and opaque. The upper lobe was slightly aerated. The iodized oil was still visible in the bronchi.

On June 19, the improvement was maintained; the weight was increased. The wound was small, about the size of a pencil. With the thoracoscope introduced in the orifice of the fistula, four bronchial openings, well epidermized, were seen. A roentgenogram (fig. 12) showed an advanced aeration of the upper lobe with absence of any indication of abscess.

On Aug. 20, 1929, the patient felt perfectly well, did not cough or expectorate, and performed her duties of mother and housekeeper. She was in the seventh month of pregnancy. A tube the size of a Dakin tube was still maintained in

Fig. 11 (case 2).—Graded thoracoplasty, phrenicotomy and cautery pneumocotomy, forty-eight days after the last stage (March 1, 1928).

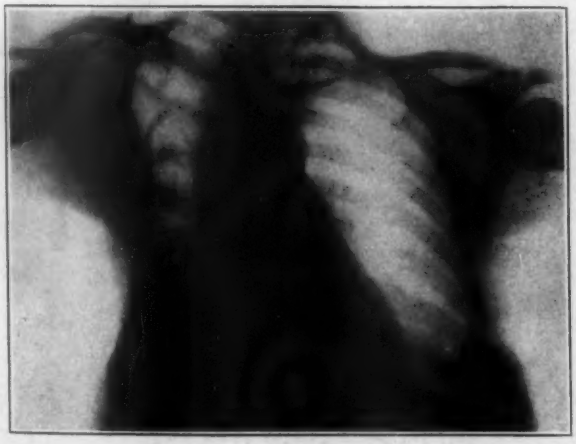

Fig. 12 (case 2).—Seventeen months after operation. The remainder of the right lung has expanded in the upper part of the right side of the chest (June, 1929).

Fig. 13 (case 2).—Twenty months after operation. Expansion of the remaining parenchyma of the lung is still more accentuated on the side operated on (September, 1929).

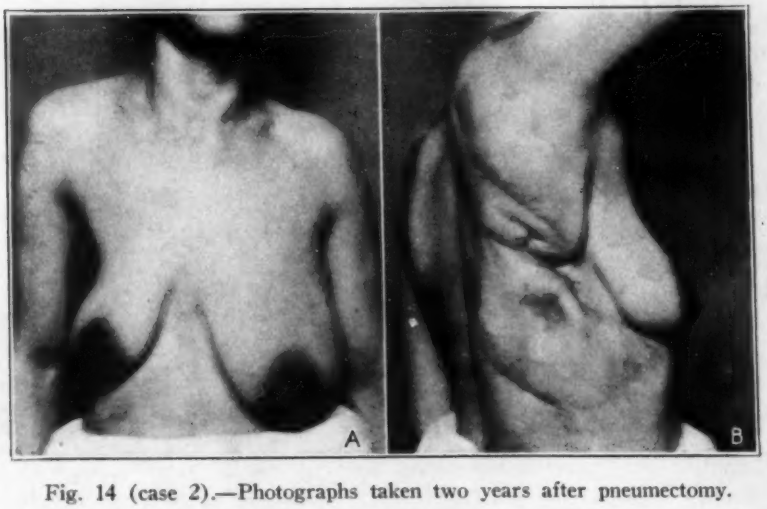

Fig. 14 (case 2).—Photographs taken two years after pneumectomy.

place, although there was no more discharge. The patient had gained 39 pounds (17.7 Kg.) since being discharged from the hospital. A roentgenogram (fig. 13) showed a remarkable progress in the aeration of the remaining parenchyma of the right lobe, which filled up what was left of the thoracic cavity on the side that had been operated on. On Jan. 4, 1930, the patient was in perfect condition. She had a normal delivery of a healthy baby weighing 6 pounds (2.7 Kg.), which she was nursing. (The first roentgenograms taken of this patient's lungs were lost. Only the three last are shown here.)

COMMENT

The two cases presented have several points of interest.

The first was a typical case of bronchiectasis of undetermined origin, possibly resulting from pneumonia in childhood, with frequent coughs and colds since. After every cold, the chronic condition presented a temporary exacerbation which was followed by permanent aggravation of the existing condition. Finally, a more severe pulmonary attack produced the classic symptoms of advanced bronchiectasis. A roentgenogram taken following the injection of iodized oil, several years ago, would certainly have shown bronchial dilatation already present, and a bronchoscopic examination at that time probably would have revealed incomplete drainage and possibly retention in the bronchi of the lower left lobe. Another point of interest is the absence of pleuropulmonary adhesions, although the bronchial dilatations were of considerable size, and the fact that even after the refillings were interrupted for over a month, no adhesions developed. The collapse of the lung, which had been complete for about two months, was followed by a marked improvement of only temporary duration.

Another fact of great importance is that this patient presented rather advanced lesions at the right base, besides the main lesions on the left, to such an extent that Dr. A. Miller was doubtful as to the indications for, and the outcome of, a lobectomy. However, the lesions on the right side cleared up shortly after the exeresis of the principal focus (left lower lobe) and gradually disappeared completely.

The method of obtaining the high spinal anesthesia in this case is not above criticism. I used it because of the great satisfaction it gave me in an extended experience during the Great War. I was then the first to use procaine hydrochloride instead of benzoyldimethylaminoethylpropanol hydrochloride (stovaine), which Jonesco, the pioneer in the use of this procedure, employed. The former drug does not affect the motor fibers of the mixed nerves to the same extent that the latter does, and therefore does not produce sudden paralysis of the respiratory muscles and temporary respiratory distress as does the latter drug. In thoracic wounds with the pleural cavity wide open, I repeatedly used high spinal procaine hydrochloride anesthesia in order to avoid cough

and deep inspiratory and expiratory movements provoked by inhalation anesthetics, during the induction period, the disastrous effect of which on the heart, is well known. I have had gratifying results with this method. The site of the injection, the fifth dorsal space, is not to my mind an argument against the procedure. The anesthetic is readily fixed in the posterior roots and has no tendency to go upward. Syncope is due, when it occurs, to cerebral anemia secondary to the extreme abdominal vasodilatation from paralysis of the splanchnic nerves. The patient "bleeds into his own vessels." No direct action of procaine hydrochloride, with the small dosage employed, on the centers of the fourth ventricle has so far been proved. I rather believe that deaths from spinal anesthesia are due either to the use of excessive amounts of the anesthetic or to a failure to put the patient in a slight Trendelenburg position, which insures a sufficient amount of blood both to the brain and to the territory of the vena cava, so that notwithstanding the extreme abdominal vasodilatation, enough blood comes back to the right side of the heart to insure its functioning. It is therefore less dangerous to use smaller quantities of procaine hydrochloride and inject these into the space corresponding to the metameres to be anesthetized, than to inject the anesthetic into the "safer" low spaces and use two or three times these amounts.

A last point of interest, which has already been emphasized, is the quiet respiration and undisturbed circulation despite the wide opening of the pleural cavity—which is due to the preliminary collapse of the lung. I wish to emphasize this point again because, knowing it, one operates without fear of a precipitous catastrophe and without the hindrance of a limited exposure of the operative field; this insures smoothness, speed and accuracy—indispensable factors in the success of an intrathoracic operation.

The second case pictures the postpneumonic and postempyemic type of bronchiectasis. Protracted pneumonia with the persistence of a focus of consolidation (due, to my mind, to persistent bronchial obstruction) is the determining cause of this form of bronchiectasis. Empyema does not clear up after thoracotomy because of the persistence of the infection in the underlying lung and the bronchial fistula. Repeated operations do not clear the condition because they do not strike at the cause. The existence of a more or less voluminous pleuropulmonary cavitation communicating with an internal bronchial fistula is misleading. Not until the bronchial dilatations and multiple small abscesses due to diffuse bronchopneumonitis secondary to bronchial obstruction are cleared up, can cure follow. The clinical symptoms improve when the "honeycomb" lesion is more or less sufficiently drained through a tube penetrating one of these cavities and proportionately to the extent that this

one cavity communicates with the others. The symptoms reappear whenever this drainage fails. In the meantime, the disease spreads over the lung while the surgeon wonders why the patient does not improve, although "the cavity is adequately drained." An intrabronchial injection of iodized oil solves the problem by showing the existence of bronchiectatic lesions. Only an eradication of the involved parenchyma in the chronic cases (and even then often only with the help of a permanent bronchostomy) insures a clinical cure. Bronchoscopic treatment in the early stages of the disease in this case would possibly have cleared up the affected pulmonary area. I agree with Pickhardt in considering "delayed pneumonias" cases calling for an active and early surgical treatment. When the disease has advanced, procrastination and "transference" of the unfortunate patients with the discharge note "improved" will certainly not cure them. They are doomed to certain death. Is it not better to take the only chance, which is a radical operation? Sauerbruch, Lilienthal, Meyer, Torek and their followers took these chances and have saved more lives than have the conservatives in this field. As against such conservatism, I would advocate a very conservative boldness. Only by perfecting operative procedures and decreasing the associated mortality will a solution of the problems of bronchiectasis be found. This goal can be attained by a more extensive study of the physiology of these morbid states, and it is on this ground that I have submitted these suggestions.

CONCLUSIONS

1. A clinical classification distinguishing different forms of bronchiectasis is suggested, and the practical usefulness of these distinctions has been set forth.

2. The necessity for using a prolonged and progressive treatment against a chronic and progressive disease is shown.

3. In advanced forms of bronchiectasis, only eradication of the diseased parenchyma of the lung can produce a cure. This, according to the case, should be done by resection (lobectomy), cauterization (cautery pneumectomy of Graham) or exteriorization (Whittemore).

4. In order to decrease the mortality incident to these operative procedures, a technic of "multiple stage lobectomy" is outlined in which the following stages are systematically performed in the order named: artificial pneumothorax, phrenicectomy, thoracoplasty and lobectomy.

5. In support of this method, physiologic, pathologic and clinical data have been presented.

6. Two cases of advanced bronchiectasis in which cure was achieved by the use of this technic are reported.

COMPARATIVE VALUE OF SPLANCHNIC AND SPINAL ANALGESIA IN THE TREATMENT OF EXPERIMENTAL ILEUS*

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NEW ORLEANS

About fifteen months ago, we had occasion to make a preliminary report of results obtained in the treatment for experimental ileus by the induction of splanchnic analgesia. In that communication we expressed the opinion that splanchnic analgesia was preferable to spinal analgesia, at least from the point of view of safety to the patient. From the theoretical point of view, spinal analgesia and splanchnic analgesia accomplish the same end in that they both produce a block of the splanchnic nerves. In one case (spinal analgesia) the block in the reflex pathway is made at the point of emergence of the white rami communicantes from the spinal cord, while in the other (splanchnic analgesia) the splanchnic nerves are blocked only after their complete formation as they lie in the retroperitoneal tissues anterior to the bodies of the last dorsal and first and second lumbar vertebrae. Other things being equal, chemical section of the roots entering into the formation of the splanchnic nerves, by means of spinal analgesia, should be as effective as chemical section of the nerves produced by infiltration further on in their course. At the time of our previous investigation we were not in possession of any facts indicating the relative efficiency of the two methods that are available for the production of a splanchnic block.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

In order to gain a lucid conception of what splanchnic block may be expected to accomplish with respect to restoration of motor function to a paralyzed loop of intestine, it becomes necessary to review briefly the nervous regulation of the intestinal movements. As has been appreciated from the early beginnings of physiology, the intestine is capable of normal motor activity in the absence of all extrinsic nerve control. There is some evidence, however, that the rhythmic or pendular activity of the intestinal tube is closely dependent on the nerve elements which

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enter into the formation of the so-called plexuses of Auerbach and Meissner. That the orderly, rhythmical movements of the intestine are dependent on its intrinsic nervous system, and not on any inherent power possessed by the individual muscle cell, is accepted by some observers but denied by others. Rosenstein and Köhler [1] stated that if the mucosa and submucosa are removed from a loop of intestine, the automaticity of the intestinal movement in the affected loop is not disturbed. Since the plexus of Meissner lies within the submucosa just beneath the mucosa, and the procedure of removing the submucosa detaches this plexus from the underlying musculature, it is to be presumed that the plexus of Meissner is little or not at all concerned with the intrinsic movements of the intestine. According to Rosenstein and Köhler, however, separation of the circular from the longitudinal layers of the muscular coat of the intestines destroys the automatic activity of the circular fibers, but does not affect the automaticity of the longitudinal fibers. Gunn and Underhill,[2] Alvarez and Mahoney [3] and von Esoeld [4] were not in agreement with this view of the intrinsic nerve regulation of the intestine, since they found that the circular muscular layer when deprived of its associated nerve net continues to show the function of automatic rhythmicity.

The extrinsic, or regulatory, nerve supply to the intestine is derived partly from the vagi and partly from the splanchnic nerves. Gaskell,[5] Macleod,[6] Bayliss and Starling [7] and others have presented evidence to show that the primary action of the vagi is motor, while the action of the splanchnic nerves is essentially antagonistic and performs the function of inhibition. Bayliss and Starling [7] have shown that stimulation of the vagi causes a preliminary inhibition, but Hotz [8] made the observation that the stimulation of any sensory nerve produces an

1. Rosenstein, P., and Köhler, Hans: Ueber die Beinflussung der Darmparalyse durch Nikotininjektion in das Ganglion Coeliacum, Deutsche Ztschr. f. Chir. **210**:315, 1928.

2. Gunn, J. A., and Underhill, S. W. F.: Experiments upon the Survival of Mamalian Intestine, Quart. J. Exper. Med. **8**:275, 1914.

3. Alvarez, W. C., and Mahoney, L. J.: Myogenic Nature of Rhythmic Contractions of Intestine, Am. J. Physiol **59**:421, 1922.

4. Von Esoeld, L. W.: Verhalten von plexushaltigen und plexusfreien Darmmuskelpräparaten, Arch f. exper. Path. u. Pharmakol. **134**:357, 1928.

5. Gaskell, W. H.: The Involuntary Nervous System, New York, Longmans, Green & Company, 1916.

6. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, St. Louis, C. V. Mosby Company, 1922.

7. Bayliss, W. B., and Starling, E. H.: Preliminary Note on the Innervation of Small Intestine, Proc. Physiol. Soc. Lond. **24**:122, 1899.

8. Hotz, Gerhard: Beiträge zur Pathologie der Darmbewegungen, Mitt. a. d. Grenzgeb. d. med. u. Chir. **20**:257, 1909.

initial inhibition of intestinal movement. Since the vagi contain a certain number of sensory fibers, preliminary inhibition, as a result of stimulation of these nerves, is to be expected. Hotz [8] expressed the belief that inhibition is produced by way of the splanchnic nerves, since he found that mechanical section of these nerves produces augmentation of intestinal movements. Stimulation of the splanchnic nerves produces an initial inhibition presumably due to the fact that they contain sensory fibers, but increased motility ensues thereafter, and this effect is both pronounced and prolonged, indicating that the essential function of the nerve is one of inhibition.

Our experimental results have been fully in accord with the views expressed by the foregoing authors. We have repeatedly and invariably

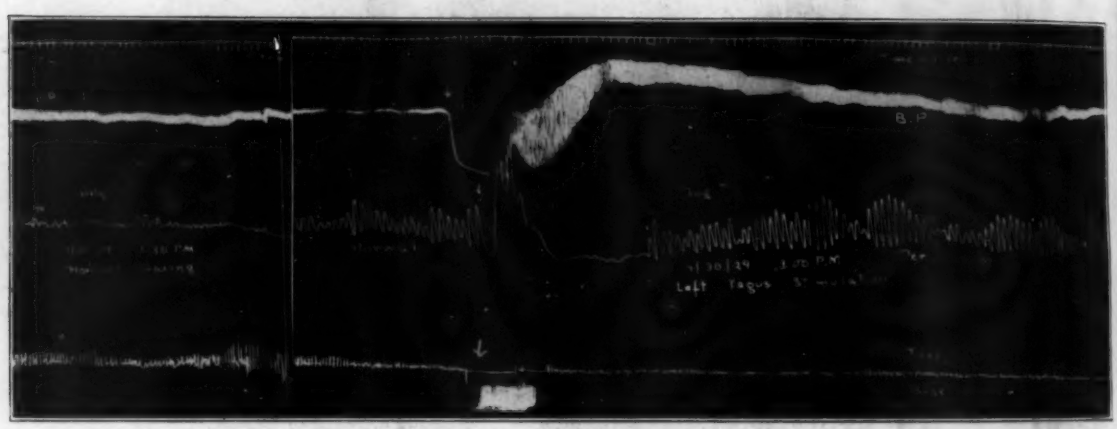

Fig. 1.—Kymographic tracing, showing normal intestinal movement, blood pressure readings and respiration. The left vagus nerve was stimulated by means of a faradic current at the point shown by the arrow. This produced a temporary cessation of the heart beat as shown in the upper curve. A temporary cessation in intestinal movement also occurred, associated, however, with an increase in intestinal tone. In this particular instance, following the return of intestinal tone to normal, intestinal movement was resumed, and after about thirty seconds became more active than before.

found that stimulation either of the right or of the left vagus nerve in the neck, whether by mechanical or by electrical means, produces a definite increase in the amplitude of intestinal movements. This effect, however, is characteristically seen only after an initial period of inhibition, which lasts for a varying period of time, but usually for only one minute or less. An initial increase in tone of considerable magnitude is characteristically seen in the intestine within from five to ten seconds after stimulation. This phase, however, is also only transitory (figs. 1 and 2). The initial increase in tone and the subsequent short

period of inhibition of intestinal movement, as previously described and as shown in figures 1 and 2, are not peculiar to stimulation of the vagus nerve as such, but occur whenever sensory nerves in any part of the body are stimulated. Thus the introduction of the point of a needle during splanchnic analgesia, any dissection, as, for instance, the isolation of a blood vessel, or any pinching or squeezing, as during the course of the application of a hemostatic forceps, produces an exactly similar effect. For this reason we must assume, with Hotz, that the preliminary inhibitory phase of vagus stimulation is the result of an action on the sensory fibers rather than on the motor fibers of which the vagus nerve is composed. Conversely, cutting of the vagi

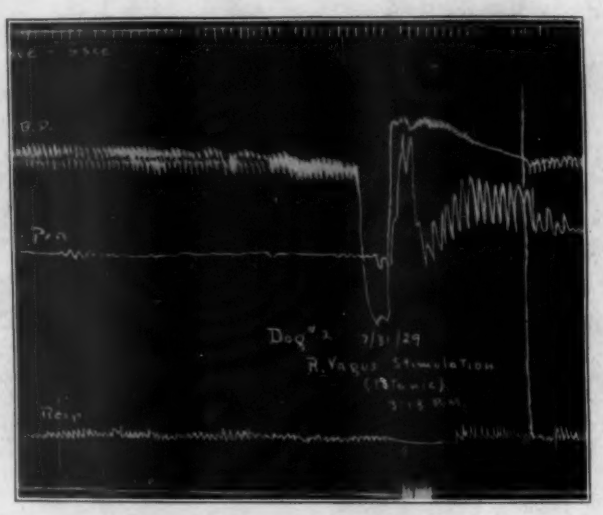

Fig. 2.—Kymographic tracing, showing the effect produced by stimulation of the right vagus nerve with a faradic current. Immediately following this stimulation there was a cessation of intestinal movement, associated with a definite increase in intestinal tone. After the return of intestinal tone to normal, the intestinal movement became much more active than before stimulation.

has been found to produce a decrease in the amplitude of intestinal movements, preceded, however, by a transitory increase in motility which presumably results from the transitory mechanical stimulation incident to the section. Moderate decrease in motility is noted after the section of one vagus nerve, but when both vagi are cut, the effect is still more noticeable (fig. 3). This diminution of intestinal movement lasts for a variable period of time, after which the intestine tends to resume its normal motility, the nerve motor-inhibitor mechanism apparently being capable of readjusting itself with a fair degree of rapidity following the loss of either one or the other of its two antagonistic sets of regulatory nerves.

Stimulation of either the right or the left greater splanchnic nerve tends to produce a cessation of intestinal movement and loss of tone. In favorable cases intestinal movement can be made to cease almost entirely (figs. 4 and 5). Although the inhibitory effect of such stimulation is definite, as shown in figures 4 and 5, it represents stimulation of the greater splanchnic nerve only, the lesser splanchnic nerve being exceedingly difficult to isolate because of its anatomic relations.

Cutting of the greater splanchnic nerves is followed by a definite increase in tone and an amplitude of intestinal movements, as shown in figure 6.

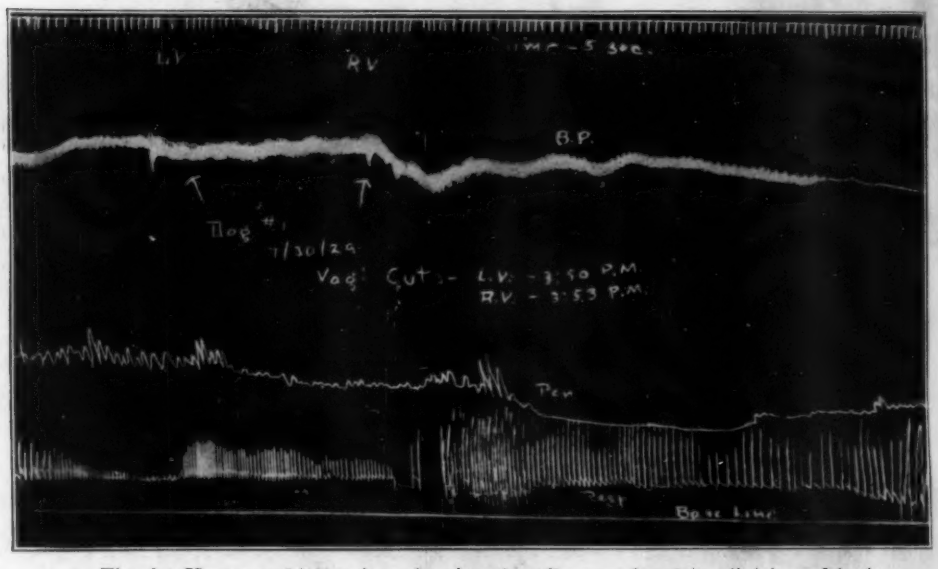

Fig. 3.—Kymographic tracing, showing the effect produced by division of both vagus nerves. Immediately following the cutting of each nerve there was a slight increase in intestinal movement, which was followed, after about one minute, by almost complete cessation of all intestinal movements, as well as loss in tone.

Following division of either the vagus or the sympathetic nerve supply, the effect of stimulation of the antagonistic pair of nerves shows a highly exaggerated effect. Thus, after section of the splanchnic nerves, stimulation of the vagi produces an unusually marked increase in amplitude of intestinal movements (fig. 7), and stimulation of the splanchnic nerves, after vagotomy, tends to produce relatively profound inhibition.

Theoretically, any therapeutic measure aimed at the restitution of motor activity to a paralyzed intestine might take as its point of departure: (1) the muscle cell itself, (2) the intrinsic nervous system of the intestine (plexuses of Auerbach and Meissner) or (3) the

extrinsic nerve supply, viz., the vagus nerves and the splanchnic nerves. Considering only the extrinsic nerve supply, any attack directed against the vagi must, of necessity, involve stimulation, whereas a similar attack directed against the splanchnic nerves must involve paralysis.

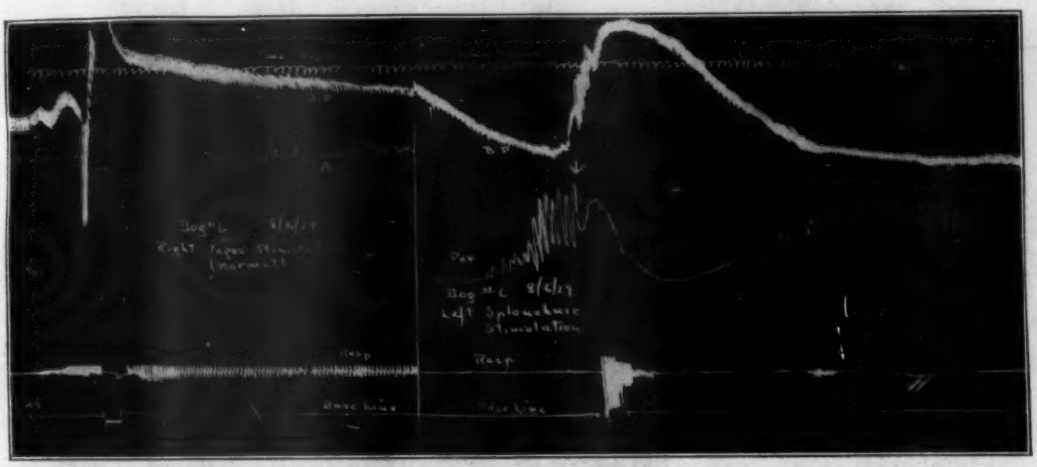

Fig. 4.—Kymographic tracing, showing the effect of stimulation of the left greater splanchnic nerve on blood pressure and intestinal movement. As indicated by the arrow, the left splanchnic nerve was stimulated with a faradic current when intestinal movement was active. This produced an immediate rise in blood pressure which returned to normal after about two minutes. There was an immediate cessation of all intestinal movement, and a temporary increase in intestinal tone, followed by a marked loss of tone.

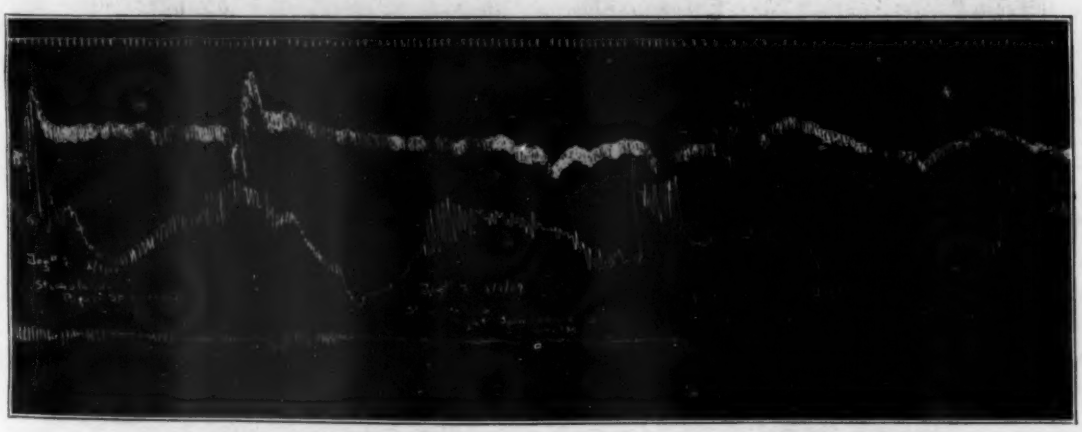

Fig. 5.—Kymographic tracing, showing the effect of stimulation of the greater splanchnic nerves on blood pressure, intestinal movement and intestinal tone. The tracing shows three successive stimulations of the right greater splanchnic nerve; a repetition of effect results, i. e., a momentary rise in blood pressure, an immediate cessation of all intestinal movements and a loss of intestinal tone.

Interruption of impulses traveling centrifugally along the splanchnic nerves may conveniently be performed in two places by chemical means: the first, at the point where the white rami communicantes leave the spinal cord by way of the ventral or motor root; the second, in the retroperitoneal space in the region of the first lumbar vertebra, where the nerves enter into the formation of the semilunar ganglia and the greater, lesser and least splanchnic plexuses. Chemical section of the roots entering into the formation of the splanchnic nerves is technically not difficult, since it involves merely the introduction of an anesthetic solution sufficiently high into the subarachnoid space to anesthetize the segments of the cord from the fifth dorsal to the first

Fig. 6.—Kymographic tracing, showing the effect produced by division of the splanchnic nerves. At the point marked by *R*, the right splanchnic nerve was divided, and at the point indicated by *L* the left splanchnic nerve was divided. Following division of the right splanchnic nerve intestinal movement, which had been active previously, became almost completely abolished. About three minutes after division of the left splanchnic nerve, the intestinal movements became hyperactive. The tone of the intestinal muscle becomes markedly increased. There is also a definite decrease in the blood pressure, which is gradual.

lumbar vertebra. Such a procedure is, of course, commonly employed in operations on the organs lying in the upper part of the abdomen. Actually the performance of spinal analgesia is not without danger, not only from the point of view of infection, to which the leptomeninges are particularly susceptible, but also from the point of view of intradural hematoma formation and mechanical injury to the cord, which could occur, of course, only in those cases in which puncture is made at a higher level than the termination of the cord, although in this con-

nection the considerable variation in the level of the position of the conus medullaris must be remembered. With respect to the level attained as a result of spinal analgesia, it must be borne in mind that an anesthetic solution once introduced into the dural sac cannot be removed, and the height which anesthesia may attain is, therefore, only partly within the control of the anesthetist.

Splanchnic analgesia by the posterior route, that is, according to the technic of Kappis,[9] although technically a somewhat more formidable procedure than that of spinal analgesia, is relatively devoid of danger when carefully performed, and for this reason seems a more logical

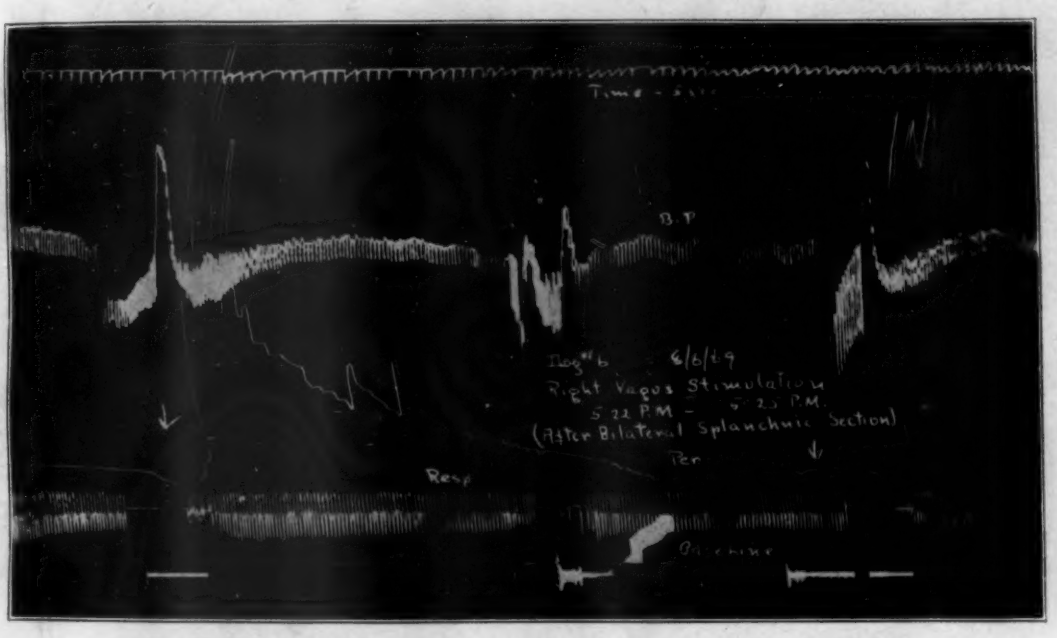

Fig. 7.—Kymographic tracing, showing the effect of vagus stimulation on intestinal movement after bilateral splanchnic section. At the point indicated by the first arrow, the right vagus was stimulated by a faradic current. Immediately following each stimulation there was a marked increase in intestinal tone, as well as intestinal movement, no movements having been noted previous to these stimulations.

procedure. Of the drugs used in producing spinal analgesia, only those having a local anesthetic action are suitable. When the method of splanchnic analgesia is used, however, not only anesthetic substances but any drug which is capable of interfering with the transmission of impulses through the sympathetic ganglia may be used, for example,

9. Kappis, M.: Erfahrungen mit Lokalanesthesie bei Bauchoperationen, Verhandl. d. deutsch. Gesellsch. f. Chir. **43**:87, 1914.

nicotine, which presumably exerts no effect on the nerve trunk itself, but paralyzes the synaptic junction in the semilunar ganglia.

The present report concerns particularly a consideration of the relative merits of spinal and splanchnic analgesia, and, as far as splanchnic analgesia is concerned, with the relative merits of the drugs procaine hydrochloride and nicotine. The experimental results reported were obtained from a series of seventy dogs. Most of these animals were rendered anesthetic prior to operative manipulation by the introduction of from 0.18 to 0.3 Gm. of sodium barbital per kilogram of body weight through a stomach tube, but in several animals ether anesthesia was used. All the experimental data have been recorded by kymographic tracings, and are, therefore, we believe, of far greater value than deductions from unaided ocular observations, however carefully the latter may be made. The operative technic consisted of laparotomy, followed by the introduction, through a small incision in the intestine, of a thin walled, rubber balloon into the lumen of the intestine, the balloon being connected by means of a small rubber tube to a "Marey tambour" arranged to record, by means of a lever and writing point, on a lightly smoked kymographic drum. In every case concomitant blood pressure tracings were obtained from the carotid artery by means of cannularization, pressure variations being conducted through a system of rubber tubes filled with sodium citrate solution to a mercury manometer, which, in turn, was provided with a "rider" and a recording point. Respirations were also recorded by means of a recording point, actuated by a tambour and connected by a rubber tube to a tracheal cannula. In almost all the cases the vagi were dissected free during the course of the operative manipulation incidental to the insertion of the carotid and tracheal cannulas. In certain cases in which the splanchnic nerves were isolated, the operative approach was through the flank in the region of the costovertebral angle, and access was thereby gained to the retroperitoneal space without perforation of the posterior parietal peritoneum. For the most part, the operative procedures incident to the opening of the abdomen and the placing of balloons within the lumen of the intestines were performed in a bath of warm saline solution. In this manner, the peritoneum and the contents of the peritoneal cavity were protected from exposure to the air and chilling.

SPLANCHNIC ANALGESIA (NICOTINE)

Because of the beneficial effects of spinal analgesia in the treatment for ileus observed by others, Rosenstein and Köhler [10] conceived the

10. Rosenstein, P., and Köhler, Hans: Therapeutische Versuche zur Bekämpfung der Darmlämung durch Umspritzung des Ganglion Coelicum, Med. Klin. **22**:530, 1926.

idea that if the splanchnic nerves were blocked by some substance which would be specific for these nerves, patients with ileus might be even more effectively treated. Because nicotine is supposedly specific in its action on sympathetic ganglia, its action being that of paralysis of the synaptic junctions, these investigators employed this drug both experimentally and clinically. They reported their results on twenty-two normal rabbits. In this group of animals and in six additional rabbits in which peritonitis had previously been produced by the injection of pure cultures of streptococci, they injected various drugs into the region of the celiac ganglia, but among these drugs nicotine was conspicuous by its absence. These particular experiments are described by Rosenstein and Köhler [1] in great detail. The experiments that they supposedly performed with nicotine are mentioned only briefly and are not described in detail; they stated merely that the results obtained by the injection of nicotine into the splanchnic area are "similar" to those obtained by the injection of other substances, including procaine hydrochloride. Rosenstein and Köhler reported twenty-six clinical cases of ileus in which the patients were treated by the injection of nicotine "into the celiac ganglia." Seventeen of the twenty-six patients were relieved of their ileus; nine, however, subsequently died. These authors expressed the opinion that in nine cases, in which no increase in peristaltic activity was obtained, an inactive nicotine salt had been injected.

In order to verify the results obtained by Rosenstein and Köhler,[1] the following experiments were performed. In nine dogs, a nicotine solution was injected into the splanchnic area. In two animals two injections were made. In all cases a balloon was inserted, as previously described, into the duodenum, ileum, and colon, respectively. In eight of the nine animals, the nicotine solution was injected into the splanchnic area, according to the technic of Kappis, within a short time after the stimulation of the vagi with the faradic current. The ninth animal had received two prior injections of procaine hydrochloride into the splanchnic area before the nicotine solution was injected. The results obtained in the latter case, however, correspond with the general results obtained in the other cases. The effect produced by the introduction of a nicotine solution into the splanchnic area was as follows: There was a marked and constant increase in blood pressure, which, with the exception of three instances, was always greater than 90 mm. of mercury. This blood pressure effect was transitory, however, lasting not more than three minutes, the pressure thereafter returning to, or falling slightly below, normal (figs. 8 and 9). The amount of nicotine administered was always 1 minim (0.06 cc.) (except in three instances), since this amount was the utmost that was considered safe to give. In

one case in which 0.5 minim (0.03 cc.) was given, there was a blood pressure increase of only 10 mm. of mercury. In one case in which 10 minims (0.60 cc.) was given, there was an increase of considerably more than 154 mm. of mercury (the utmost capacity of the manometer), the rise in pressure being so rapid and great that the mercury was forcibly ejected from the free arm of the manometer. A third animal showed no remarkable effect from the injection of 2 minims (0.12 cc.) of nicotine in divided doses. In each instance the given amount of nicotine was diluted with 20 cc. of distilled water, 10 cc. of this solution being injected on either side into the splanchnic area. This corresponds to the technic employed in splanchnic analgesia obtained with procaine hydrochloride in which relatively large amounts of fluids must be used

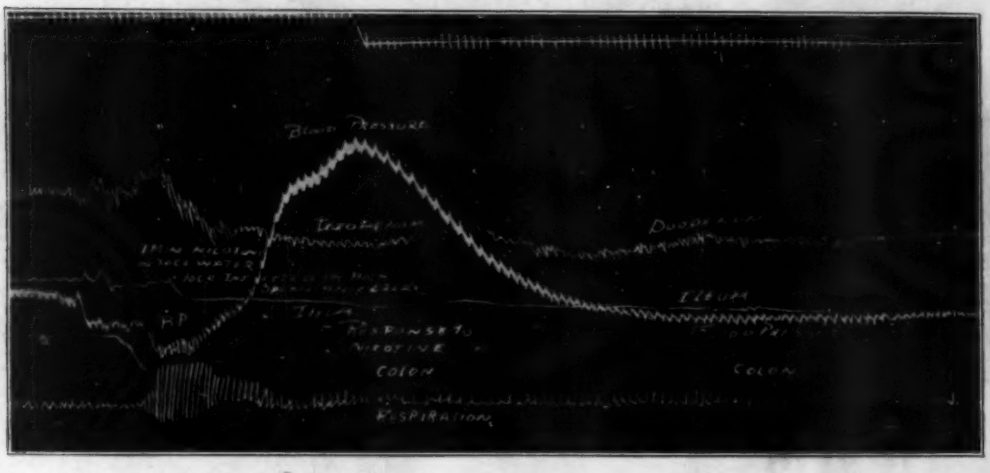

Fig. 8.—Kymographic tracing showing the effect on blood pressure and intestinal movement of the introduction of nicotine into the splanchnic area. The most marked effect was a progressive and marked rise in blood pressure; the blood pressure fell to normal about three minutes after having reached its greatest height. There was a marked increase in respiration which temporarily increased the pressure in the duodenum; the intestinal tracing was complicated by a superimposed respiratory component. There was a decrease in tone in the ileum, and six minutes after the administration of the nicotine a definite but temporary increase in intestinal movement was noted.

to allow for unavoidable variations in the position of the point of the needle, through which the solution is injected. Owing to the depth of the injection, it is obviously impossible to direct the point of the needle accurately into the ganglion itself. The best that can be anticipated is a deposition of the solution somewhere in the immediate vicinity of the ganglion. Rosenstein and Köhler,[1] in their experimental work on rabbits, injected the nicotine solution directly into the celiac ganglion

through a laparotomy incision after complete evisceration of the abdominal contents, a procedure which is obviously impossible in the clinical treatment of the average patient with ileus. When splanchnic analgesia is performed clinically with nicotine, these investigators advocate a modification of the original Kappis technic in that the point of the needle is thrust several millimeters beyond the ventrolateral surface of the body of the vertebra. Such a procedure is distinctly dangerous because of the likelihood of wounding the inferior vena cava or aorta. These authors stated that it is not only possible but necessary to inject the nicotine solution directly into the ganglion, a procedure which is obviously chimerical.

In our series of experiments the effect on the duodenum, ileum and colon produced by the introduction of the nicotine solution into the splanchnic area was inconstant, with respect to both changes in the intestinal tone and the amplitude of intestinal movements. In five cases

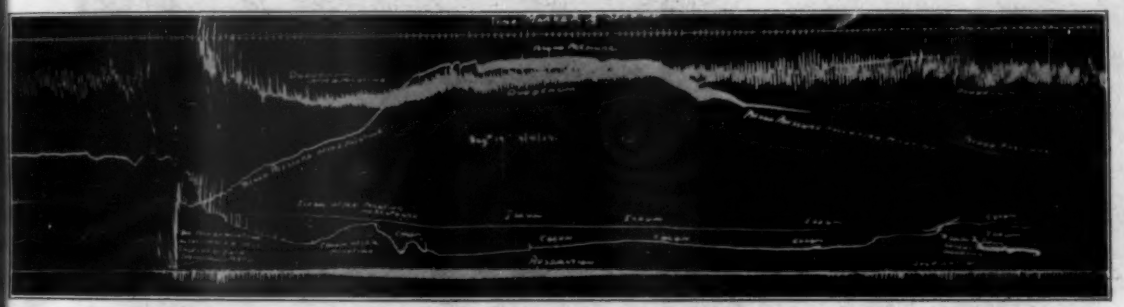

Fig. 9.—Kymographic tracing, showing the effect produced by the introduction of nicotine into the splanchnic area. As shown by the lowermost tracing, a definite increase in respiratory movement resulted. The duodenal tracing, which is the second from the top, was complicated by a superimposed respiratory component. The blood pressure tracing showed a typical gradual progressive rise, which reached a maximum after about four minutes, remained elevated for two and one-half minutes and returned gradually to normal. There was no change in either intestinal movement or tone in the ileum. The colon, however, showed a slight increase in tone.

the tone of the ileum was increased between 10 and 50 mm. In only one case did the colon show any increase in tone (20 mm.). In all the other cases in which a change was noted it was in the direction of a decrease, which in no case was greater and usually was considerably less than 15 mm. With respect to the effect of peristaltic movements on amplitude, negligible effects were usually seen. In one case, however, an increase of 10 mm. was noted in the ileum, and in another case a decrease of 10 mm. in the colon; otherwise. changes varied from 1 to 3 mm.

From these results we are forced to conclude that nicotine when injected into the spanchnic area is probably of little or no value in the treatment for ileus. It is conceivable that the injection of nicotine directly into the semilunar ganglion might produce more pronounced effects than we have been able to obtain by diffusion of the solution. However, diffusion is the only method that is clinically available and safe. Furthermore, the injection of nicotine is open to serious objections in that it produces rapid and exaggerated increases in blood pressure. While this hyperpiesis might be tolerated with impunity by young persons and those with normal vascular systems, it might prove disastrous to patients with an abnormally high blood pressure and especially to those with vascular lesions.

SPLANCHNIC ANALGESIA (PROCAINE HYDROCHLORIDE)

Our experimental experience with splanchnic analgesia obtained with procaine hydrochloride now extends over a series of fifty animals. Splanchnic analgesia has been induced in all cases by the posterior route, according to the technic of Kappis.[9] In the experiments reported in a previous contribution,[11] all of the observations were made on animals having experimentally produced intestinal obstruction. The present series of experiments includes normal animals and also ones in which mechanical obstruction had been present for varying lengths of time. In our previous investigation tracings were obtained from the ileum alone. In the present series tracings were obtained of movements in the duodenum, ileum and colon in a number of animals, the three balloons being used coincidentally.

Although the technic of the introduction of procaine hydrochloride solution for the production of splanchnic analgesia has been the same in all of our experimental investigations, the quantity of solution so introduced and the strength of the solution have varied somewhat. Our original observations were made, for the most part, on animals that had received 20 cc. of a 1 per cent solution of procaine hydrochloride bilaterally. In subsequent cases, we have most frequently used 10 cc. of a 2 per cent solution of procaine hydrochloride bilaterally. In a few instances, as little as 5 cc. on either side has been used.

In general, following the induction of splanchnic analgesia by procaine hydrochloride similar changes in intestinal motility and tone are noted in both normal and obstructed animals. The obstructed animals show a distinct tendency to react more actively than the normal ones. Much more constant and noteworthy effects are shown by the intestines of the animals in which only one balloon has been introduced. How-

11. Ochsner, A.; Gage, I. M., and Cutting, R. A.: Treatment of Ileus by Splanchnic Anesthesia, J. A. M. A. **90**:1847 (June 9) 1928.

ever, animals into whose intestinal canals three balloons have been introduced show unmistakably similar motor effects. This observation is interpreted as evidencing the inhibitory effect produced by trauma on intestinal movements, since the operative manipulation required to introduce the three ballons represents not only the trauma of three enterostomies, but also such injury as must inevitably be inflicted during the course of traction on the mesentery and surrounding structures incident to the isolation and identification of the various parts of the intestinal tract on which enterostomy is to be performed. Motor effects on the intestines of both normal and experimentally obstructed animals included not only a rise in the tone of the intestine, which in most cases was considerable, but also a somewhat spectacular increase in intestinal movements (figs. 10 and 11). In a certain number of cases, splanchnic

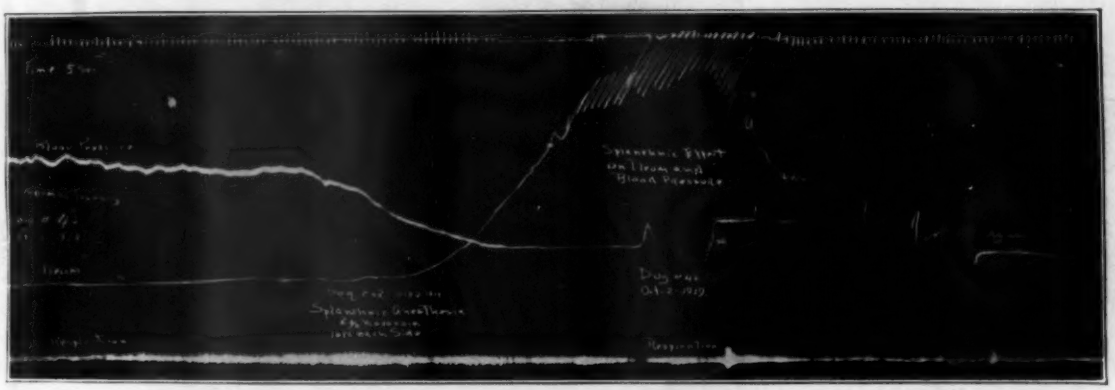

Fig. 10.—Kymographic tracing, showing the effect produced by splanchnic block with procaine hydrochloride. Following the production of splanchnic analgesia, there was a typical decrease in blood pressure, which was followed after one and one-half minutes by a marked increase in intestinal tone, and this, in turn, was followed, after an additional minute, by a definite increase in intestinal movements. The increase in intestinal tone was only temporary, lasting about three minutes. The increase in intestinal movements, however, persisted.

analgesia has been unsuccessful in restoring motility to a paralyzed intestinal musculature. Failures, when encountered, have usually been due to lapses in technic in the injection of the anesthetic solution. This has been evidenced by the fact that the blood pressure has remained unaffected. Splanchnic effects have never been noted in the absence of blood pressure changes. In a few cases, although the blood pressure has shown characteristic diminution, the motor activity of the intestine has been unaffected. In no case in which splanchnic analgesia has failed to produce characteristic motor effects in the intestine, however, has any other maneuver which we have been able to employ been suc-

cessful in restoring motor activity. This is equivalent to saying that splanchnic analgesia has been the most successful agent in the production of intestinal movements that we have been able to employ.

Because of the mechanical features that we have used in recording intestinal activity, actual measurements are of merely relative value, since the size of the balloon used in the lumen of the intestine, as well as the leverage applied to the writing point on the kymographic drum, has been subject to minor variations, over which the experimenters have had incomplete control. In eight animals in which the ileal tracings alone were attempted, a constant rise was recorded in the tone of the intestine, with the single exception of one animal, in which both splanchnic nerves had previously been cut, which animal, therefore, presented an excellent control for the other experiments. The average increase in tone on the kymographic tracing was 29.5 mm. As previously stated, the latter figure is of only relative significance, but the evaluation of the figure may perhaps be appreciated when it is

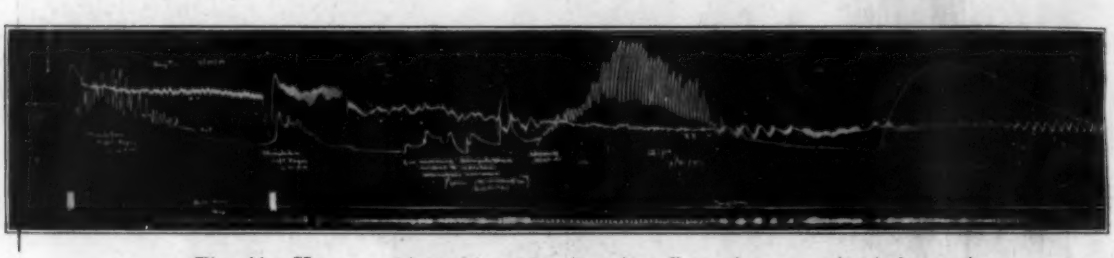

Fig. 11.—Kymographic tracing, showing the effect of vagus stimulation and splanchnic analgesia. At the extreme left of the tracing a typical reaction in both the ileum and the blood pressure was produced by stimulation first of the right and then of the left vagus nerves by means of a faradic current. In the center of the tracing the animal was turned and a splanchnic analgesia was produced. There followed a slight fall in blood pressure, which, however, was not marked. After about one and one-half minutes there was an increase in intestinal movement, followed by a marked increase in intestinal tone. This increase in tone lasted about one and one-half minutes, at which time the tone became greatest. The tone then fell for an additional two minutes, and reached its lowest level at the end of this period. Intestinal movement persisted for an additional two minutes. Three and one-half minutes after the tone of the intestine had assumed a normal level, the tone again increased remarkably without, however, any evident increase in intestinal movement. This increase in tone is similar to that observed in the first instance.

realized that with the use of the same system and the same application of leverage the normal amplitude of intestinal movement was represented by an excursion of the lever which was not ordinarily greater than from 3 to 4 mm. In addition to this rather spectacular increase in tone, the amplitude of intestinal movement itself is invariably increased after the production of a successful posterior splanchnic anal-

gesia. In these eight animals, the average increase in the amplitude of movement, as recorded on the drum, was 11.2 mm.

As to the average duration of the effect of posterior splanchnic analgesia obtained with procaine hydrochloride, the increase of tonus is considerably more transitory than the increase of intestinal movement. The total duration of the motor effect of posterior splanchnic analgesia varies considerably. It has ordinarily been not less than from five and one-half to six minutes, and occasionally has been seen to persist for as long as one-half hour or more. The duration of the spectacular rise in tonus ordinarily lasts for only from three to four minutes, although occasionally somewhat longer. Although the motor effect of posterior splanchnic analgesia on the intestinal motility is never noted in the absence of diminution in blood pressure, there seems to be no constant relationship between the amount of the blood pressure effect and the magnitude of the changes in intestinal tonus and movement. Sometimes animals showing rather insignificant decreases in blood pressure manifest spectacular changes in intestinal tone and motility, while animals showing radical decreases of blood pressure may show rather insignificant motor and tonus changes. On an average, the amount of decrease of blood pressure noted in our experimental dogs has been 20 mm. of mercury. However, characteristic motor and tonus changes have been noted in animals showing a decrease in blood pressure of only 2 or 3 mm., while certain animals have shown decreases of from 50 to 56 mm. of mercury.

When the effects of posterior splanchnic analgesia produced by procaine hydrochloride on the duodenum, ileum and colon, as shown in those animals in which balloons were introduced coincidentally into different parts of the intestinal tract are compared, the effect on the ileum is much more striking than the effect on either the duodenum or the colon. No changes of significance have been noted in the colon in respect to either tonus or motility. This observation is not inconsistent with what is known concerning the innervation of the colon. The splanchnic analgesia discussed in these experiments is not calculated to interfere with the splanchnic fibers that supply the lowermost part of the intestinal tract. In fact, it is doubtful that colonic movements are under the same sort of dual innervation as the more cephalad portion of the gut. It has been stated that the splanchnic fibers supplying the colon act in both a motor and a sensory capacity. According to Langdon Brown,[12] however, the nerve supply of the large bowel is derived from the pelvic visceral nerve and the inferior mesenteric ganglion, the former being motor, the latter inhibitory.

12. Brown, Langdon: The Sympathetic Nervous System in Disease, London, Henry Troude and Hodden and Houghton, 1923.

The effect of splanchnic analgesia on the duodenum is considerably more variable than is the effect on the ileum. As previously stated, when the "three balloon technic" was used, the results of splanchnic analgesia were relatively inconstant, but this inconstancy was noted particularly in the duodenum as compared with the ileum. As a rule, increases in duodenal tone and movement apparently are caused by splanchnic analgesia obtained with procaine hydrochloride. In some cases increases in tone have been very great. In one case this amounted to 40 mm., but usually the increase was not greater than 5 mm. These values, like the values given previously in the discussion of the effects on the ileum, are of only relative significance, but the balloon, the connection and the system of levers were purposely made as similar as possible in all cases, so that a fall or a rise of a given number of millimeters in the duodenum can be compared fairly with a similar rise or fall in either the ileum or the colon. In some instances, the effect of splanchnic analgesia on the duodenum apparently was expressed in a decrease of tone. In one instance, this was 20 mm. and in another instance 10 mm., but these values seem to represent exceptions to the general tendency. The effect on movement in the duodenum was not particularly significant. In general, changes in the amplitude of movement in the duodenum are much less constant and of considerably less amplitude than in the case of the ileum.

Domenech [13] presented experimental and clinical evidence to show that following the induction of spinal analgesia in the dog there is a considerable, and rather immediate, augmentation of intestinal contraction, as well as an increase in the frequency of these contractions. As a result of this action, bowel contents are evacuated, and the effect persists for from one-half to one hour. This action is abolished after the injection of atropine sulphate, and paralysis of the gut ensues. A similar paralysis follows the induction of rather profound narcosis. Section of the splanchnic nerves produces an effect similar to that of spinal analgesia, which the administration of atropine also abolishes. Peritonitis, Domenech [14] believed, produces paralysis of intestinal movement as a result of an irritative reflex arising in the sensory terminations of the splanchnic nerves and relayed through the spinal cord. Spinal analgesia abolishes this reflex, and thereafter the intestine resumes its normal movements.

Because of the experimental evidence of Domenech [14] concerning the effect of spinal analgesia on the rate of peristalsis in the dog's intestines, we have carefully examined the rate of the duodenun, ileum

13. Domenech, quoted by Rosenstein, P., and Köhler, Hans: Med. Klin. **22:** 530, 1926.

14. Domenech, Olsina F.: Action de l'anesthésie rachidienne sur la motilité intestinale (étude expérimentale), Presse méd. **37:**66 (Jan. 16) 1929.

and colon both before and after the production of splanchnic analgesia with procaine hydrochloride. This rate varies in different animals from about eleven to about fifteen contractions to the minute. Contrary to Domenech's observations, when we worked with spinal analgesia, in every case the rate following splanchnic analgesia was the same as the rate preceding the analgesia. The effect of both vagus and sympathetic action on intestinal movement would, therefore, seem to be confined to the regulation of the amplitude of intestinal movements rather than the rate of those movements. As far as the experimental observations of Domenech [14] are concerned, careful examination of the tracings which he presented suggests that the movements recorded by him are not purely intestinal but have transmitted respiratory pressure changes superimposed on them. We have frequently found it impossible to obtain pure intestinal motor tracings on the kymographic drum when the intestines are within the abdomen of the experimental animal, and not infrequently, even when intestinal loops containing a balloon have been removed from the abdominal cavity and have been allowed to float freely in warm saline solution, have transmitted respiratory movements been a predominating factor in the tracing. The manner of production of these respiratory excursions and transmission of the respiratory components of the tracing are not difficult to understand. Pressure is transmitted by the descending diaphragm to the stomach and also to any loops of the small bowel which may be in the immediate vicinity. If the lumen of the small intestine contains fluid, as it always does in the case of intestinal obstruction, and to a less extent if it contains gas, pressure is transmitted mechanically not only from loop to loop but also directly along the entire extent of the lumen through the intermediation of the bowel contents. The respiratory component of a bowel tracing is apt to be more marked, therefore, in cases in which the lumen of the intestine is filled with fluid material than otherwise. If in the beginning a normal tracing of the intestinal movement is obtained, the rate being counted, and if, as the result of manipulation, the intestinal movement subsequently becomes complicated by a marked respiratory component, the latter tracing may easily be interpreted as a purely intestinal movement, the rate of which is the same as the respiratory rate. As the respiratory rate is normally considerably greater than the rate of the intestinal movement, one is always liable to be misled into thinking that the rate of intestinal movements has been increased, unless concomitant tracings of both respiratory and intestinal rates are obtained. Frequently, even with both the respiratory and the intestinal tracings on the same drum, it is difficult to say whether a pure intestinal tracing is being obtained or whether the movements of the writing point on the drum are essentially respiratory. Presumably, Domenech [14] has been guilty, in his experiments, of counting an initially

pure intestinal tracing and comparing it with a subsequent respiratory one. Only in this manner do we believe that he has been able to show a change in rate as the result of spinal analgesia.

SPINAL ANALGESIA

In order to compare the results obtained with spinal analgesia with those obtained with splanchnic analgesia, a series of dogs was used in which both spinal and splanchnic analgesias were produced. This comparison is especially valuable because of the large number of clinical observations that have been made following the induction of spinal analgesia in cases of ileus. Wagner,[15] in 1922, gave the first report of the use of spinal analgesia in ileus. Since that time numerous observations have been made, especially by the French school: Asteriades,[16] Mauclaire,[17] Lapointe,[18] Vanlande, Boppe and Okinczyc,[19] Picot [20] and Guibal.[21] Duval,[22] in 1927, collected 400 cases of acute ileus in which spinal analgesia had been used. Markowitz and Campbell [23] employed spinal analgesia in experimentally produced ileus in dogs. Their results in cases of physiologic, chemical, and traumatic ileus compare favorably with the results obtained clinically by the observers mentioned. The only investigators, besides ourselves, who have reported experiments on splanchnic analgesia are Rosenstein and Köhler,[24] who worked with rabbits exclusively. In attempting to evaluate their work, it should be appreciated that there is no comparison between the activity of the intestinal movement in the rabbit and that in the dog. While, when the abdomen is open, intestinal movements can be observed only once in a great while in the dog, these movements are invariably seen in the rabbit, and are often spectacular. They persist even after circulation

15. Wagner, G. A.: Zur Behandlung des Ileus mit Lumbalanesthesie, Arch. f. Gynäk. **192**:336, 1922.

16. Asteriades, T.: Sur le traitement de l'iléus aspasamodique postopératoire aigue par la simple rachianesthésie, Presse méd. **33**:1480, 1925.

17. Mauclaire: Apropos de la rachianesthésie dans l'occlusion intestinale, Bull. et mém. Soc. nat. de chir. **53**:472, 1927.

18. Lapointe, A.: La rachianesthésie dans l'iléus, Bull. et mém. Soc. nat. de chir. **53**:479, 1927.

19. Vanlande; Boppe, and Okinczyc: Rachianesthésie et iléus, Bull. et mém. Soc. nat. de chir. **53**:479, 1927.

20. Picot: La rachianesthésie au cours de l'occlusion intestinale, Bull. et mém. Soc. nat. de chir. **53**:486, 1927.

21. Guibal, P.: La rachianesthésie dans l'iléus, Bull. et mém. Soc. nat. de chir. **53**:539, 1927.

22. Duval, P.: La rachianesthésie dans l'iléus aigu, Bull. et mém. Soc. nat. de chir. **53**:596, 1927.

23. Markowitz, J., and Campbell, W. R.: The Relief of Experimental ileus by Spinal Anesthesia, Am. J. Physiol. **81**:101, 1927.

24. Rosenstein and Köhler (footnote 1 and 10).

and respiration have ceased, and continue for some time thereafter, often with great activity. Graphic representations of intestial movements in all of Rosenstein and Köhler's investigations have been conspicuous by their absence. An unaided visual observation of moving phenomena is notoriously subject to false interpretation, especially when preconceived notions exist in the mind of the observer as to what he expects to find.

While the technic of lumbar puncture is not particularly easy in the case of certain human subjects, in the case of ordinary experimental animals it is not only difficult but, in our experience, virtually impossible, at least in the dog. In this animal the dural sac may not ordinarily be punctured except at one point, caudal to the fourth lumbar vertebra. At this level there is a hiatus, through which a needle may be introduced, between the last lumbar vertebra and the ileum and sacrum. The spaces between all other vertebrae are occluded by overlapping laminae, which present a barrier to the point of the needle. Domenech [25] developed a technic by which he has occasionally been able to enter the dural sac by introducing the point of the needle considerably lateral to the midline and directing it medially and toward the cervical region, thereafter gradually working it between the laminae. The introduction of a needle in the ordinary manner into the only available interspace, as previously noted, is a matter of great technical difficulty, a difficulty which is scarcely appreciated when one observes the illustrations sometimes shown in books of experimental animal surgery (Haberland [26]), since the width of the dural sac at this point is scarcely greater than 2 mm. (fig. 12) and the depth of the dural sac below the surface of the skin is 4 or 5 cm., or even more, depending on the size and the weight of the dog. In a comparatively large series of animals, we have rarely been able to enter the dural sac with the point of a needle. In the case in which spinal puncture has been successfully performed, moreover, it has been found technically impossbile to keep the point of the needle accurately within the dural sac so as to enable the withdrawal of cerebrospinal fluid, and a greater refinement of technic than we have been able to command would seem to be necessary to inject successfully an amount of solution sufficient to produce true spinal analgesia. This may be partly due to the additional fact that the dural sac in this particular location is surrounded by a comparatively thick and friable fat pad; obviously the introduction of a procaine hydrochloride solution must be made with considerable force in

25. Domenech, Olsina F.: Estudio experimental y clinico de la acción de la anestesia raquidea sobre la motilidad intestinal, Rev. med. de Barcelona **7**:132, 1927.

26. Haberland, H. F. O.: Die operative Technik des Tierexperimentes, Berlin, Julius Springer, 1926.

this area, in order to insure adequate diffusion in the subarachnoid space so as to produce a spinal analgesia of sufficient height. An amount of fluid great enough to obtain this result probably always eventuates in a regurgitation of fluid through the rent in the dura into the fat pad surrounding the dural sac. Probably this cycle of events actually

Fig. 12.—The lower dorsal, lumbar and sacral portions of the spinal cord of the dog, showing an intact dura. At the lower levels the conus medullaris is visible. The marker on the left side indicates the area between the last lumbar vertebra and the sacrum, the only point at which spinal analgesia can be induced in the dog.

occurred in many of our animals, because complete relaxation of the rectal sphincters was uniformly noted, a sign which is consistently present in sacral analgesia.

We are firmly convinced that, with possibly an exceedingly rare exception, any attempt at the production of a high spinal analgesia in the dog results not in a spinal analgesia but in a sacral analgesia, which is easily mistaken for a true spinal analgesia by the unwary, especially if a concomitant blood pressure tracing is not obtained. At least we wish to go on record to the effect that in no case has any one of the three present investigators been able, even after hours of painstaking endeavor, to produce an unmistakable high spinal analgesia by the introduction of a needle through the unbroken skin in the lumbar region in the dog, the success of the operation being gaged by a typical fall in blood pressure. Because of our consistent failure to obtain a true spinal analgesia in the ordinary manner, spinal puncture, we conceived the idea of performing formal laminectomy in the upper lumbar region, thereby exposing the dura and subsequently injecting an anesthetic solution into the dural sac under the guidance of direct vision. Unfortunately, this method succeeds scarcely better in our hands than does ordinary lumbar puncture. Even with the dural sac thus exposed, it is a matter of insurmountable difficulty to withdraw cerebrospinal fluid from the subarachnoid space, and when an attempt is made to inject an anesthetic solution, the solution can be plainly seen to exude from the dural sac through the puncture opening around the needle. We have attempted, with relatively little success, to avoid this regurgitation, both by bending the needle and introducing it for a considerable distance along the subarachnoid space cephalad and also by attempting to compress the dura against the needle, mechanically. The dura of the dog tears easily, and the introduction of a needle stimulates reflex activity to such an extent that it is a matter of considerable difficulty not only to avoid producing a rent in the dura, but even to retain the point of the needle within the dural sac. The only method by which we have been able consistently to obtain a satisfactory, true, high spinal analgesia of such a nature as to give the characteristic blood pressure decrease and splanchnic block has been formal laminectomy of the last lumbar together with the first sacral vertebra, exposure of the terminal portion of the dural sac by careful dissection of the fat pad in the vertebral canal and cannularization of the dural sac in this region under direct vision.

In connection with this discussion, it must be recalled that the stimulation of any sensory nerve trunk produces an immediate slight fall in the blood pressure. Such a fall in the blood pressure is constantly noted as the result of the mere introduction of the point of a needle through the skin, even in an anesthetized animal. Such a fall in blood pressure must not be confused with the decrease produced by a correctly given splanchnic or spinal analgesia. This pseudo-blood pressure

effect occurs immediately, is relatively slight and is usually relatively quickly compensated. On the other hand, the fall in blood pressure resulting from either splanchnic or spinal analgesia is delayed for at least a half minute, and the decrease in blood pressure is gradual and inclined to be profound, while at the same time it tends to persist for many minutes.

It should be noted in connection with the works of Domenech [27] that any manipulation involving the cord, inevitably produces hyperpnea. Unless one is fully aware of this fact, one may easily misinter-

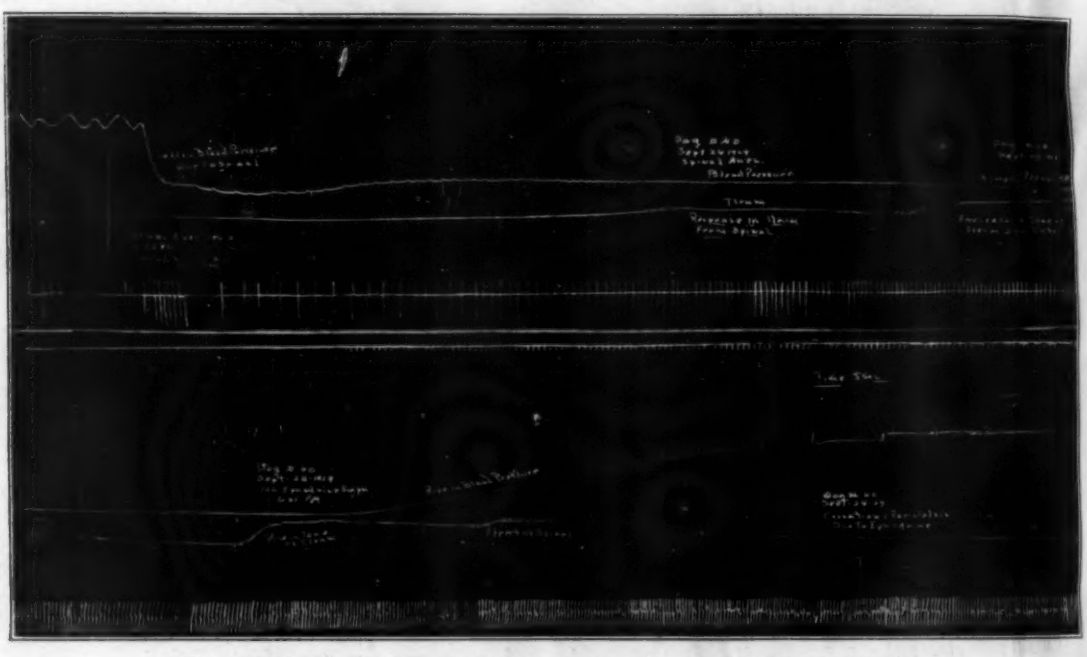

Fig. 13.—Kymographic tracing, showing the effect produced on blood pressure and intestine by spinal analgesia, and the subsequent effect produced by the administration of ephedrine. In the upper tracing a distinct fall in blood pressure was produced by spinal analgesia. After about seven minutes there was an increase in intestinal movement associated with only slight increase in intestinal tone. This persisted and was evident on the lower tracing where, at 4:05 p. m., 1 cc. of ephedrine was injected subcutaneously. Following this there was a definite increase in blood pressure, and after about six minutes there was complete cessation of all intestinal movements, as well as a loss in intestinal tone.

pret the respiratory tracing for true intestinal movement. In this manner, changes in intestinal rate may be falsely interpreted.

One further observation in connection with diminution of blood pressure observed in spinal or splanchnic analgesia is worthy of par-

27. Domenech (footnotes 13 and 25).

ticular note. Decreases in blood pressure are frequently so profound as to cause anxiety as to the ultimate survival of the animal. Under these circumstances one naturally turns to the administration of some blood pressure raising drug, especially ephedrine or epinephrine. The loss of intestinal tone following the use of these drugs is well known. Both theoretically and experimentally it is futile to expect to produce satisfactory augmentation of intestinal motility in cases in which either of these drugs has been previously administered (fig. 13).

The following conclusions are based on experiments involving thirteen animals in which spinal analgesia was produced. Because of the difficulties in technic aforementioned, only seven represented cases of undoubted pure spinal analgesia. In all cases of spinal analgesia which

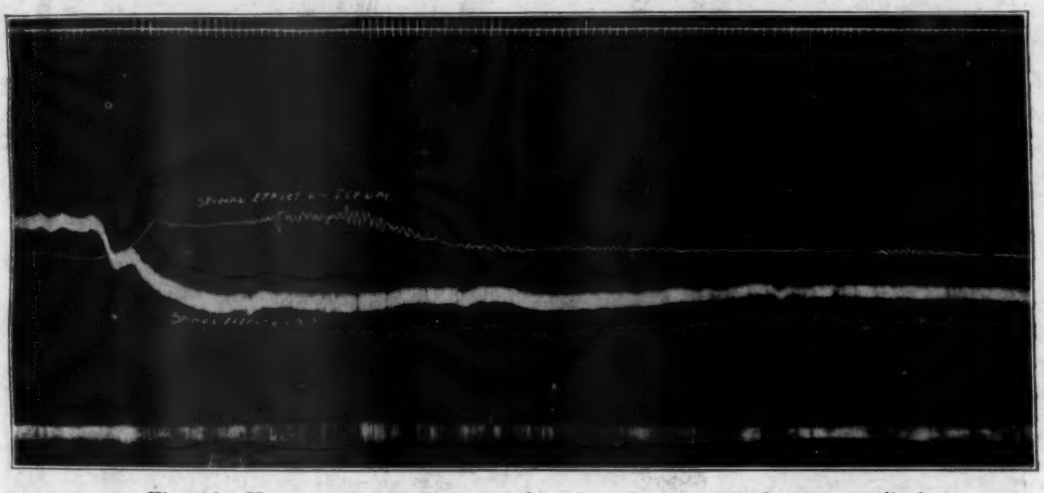

Fig. 14.—Kymographic tracing, showing the effect on blood pressure, ileal movement and ileal tone produced by spinal analgesia. Immediately following the induction of spinal analgesia, there was a definite decrease in blood pressure which was permanent. About forty-five seconds after the fall in blood pressure became evident there was an increase in intestinal tone associated with a slight increase in intestinal movement. One minute after the intestinal tone had become maximal, intestinal movement became more marked. The intestinal tone remained elevated for about three minutes, following which it fell to a normal level. The intestinal movement remained constant.

were high enough to interrupt the splanchnic fibers, definite and constant changes in the blood pressure and intestinal movements were noted. The most constantly observed phenomenon following a successfully produced spinal analgesia is a fall in blood pressure, which may occur within a half minute after the induction of spinal analgesia (fig. 13). This fall in blood pressure is usually gradual, but is more rapid than that which follows the induction of splanchnic analgesia. The fall in blood pressure

resulting from a spinal analgesia is from two to three times as great as that occurring after splanchnic analgesia.

Associated with, but invariably following, the decrease in blood pressure, an increase in tone, as well as an increase in intestinal movements, was noted after spinal analgesia (fig. 14). The increase in tone occurring after spinal analgesia is less marked and of shorter duration than that occurring after splanchnic analgesia (fig. 15). The increase in intestinal movements is, however, as constant and persists as long,

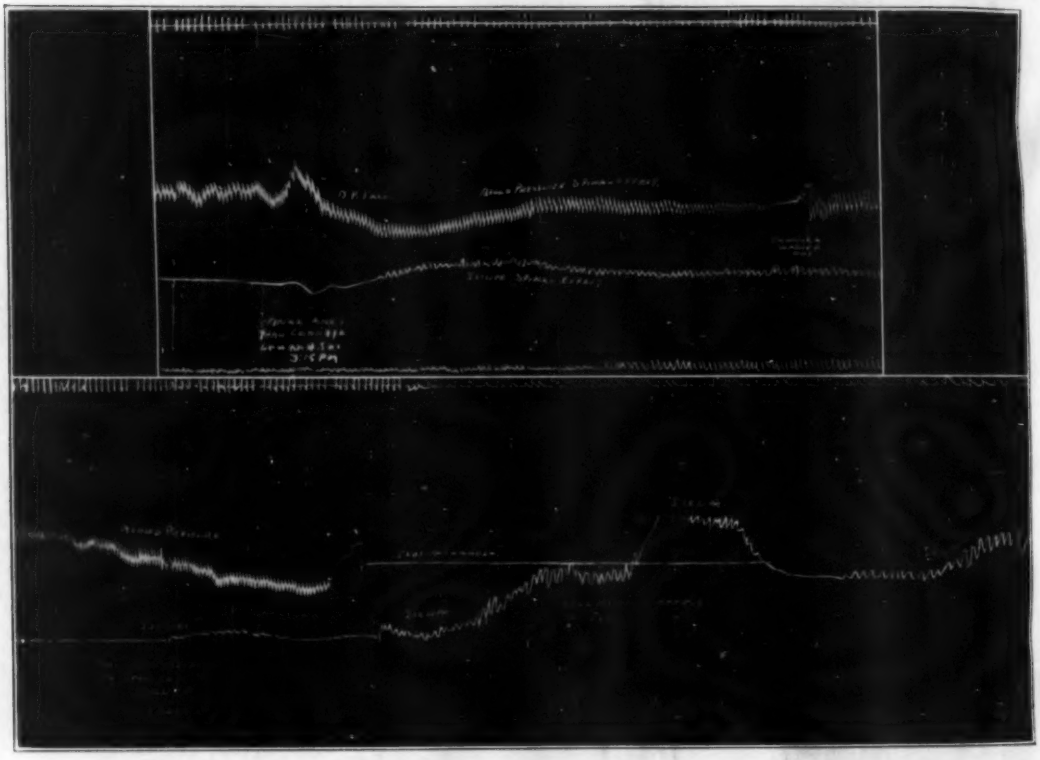

Fig. 15.—Kymographic tracings comparing the effect of spinal and splanchnic analgesia. The upper tracing showed the effect of spinal analgesia which was produced at the point indicated by the arrows. There was a decrease in blood pressure. After about one and one-half minutes there was a slight increase in intestinal tone followed by a definite increase in intestinal movement. The lower curve illustrates the effect produced by splanchnic analgesia, in the same animal, after twenty-eight minutes. A fall in blood pressure resulted, the carotid cannula becoming obstructed. After about three minutes there was a slight increase in intestinal movement. After five minutes the intestinal movement became much more marked and the tone increased rapidly; the increase in tone persisted for about five minutes, at which time a level was reached.

if not longer. The latent period of decrease in blood pressure following spinal analgesia is fifteen seconds, and the latent period of the rise in tone of the intestine, following spinal analgesia, is from thirty to sixty seconds, whereas the latent period of increase in intestinal activity is still longer, from sixty to ninety seconds. Our tracings show that the motor effects of spinal analgesia and that the prolongation of the effect of both spinal and splanchnic analgesia are more marked in the obstructed gut than in the normal gut.

The motor response resulting from stimulation of the vagus is more pronounced and prolonged after spinal analgesia than before. This corresponds with the result one would expect to obtain if the dual motor-inhibitor-vagus-splanchnic theory is correct. In other words, when chemical section of the splanchnic nerves which are inhibitory to the intestine, has been produced, the motor component of the extrinsic nerve supply to the intestine is alone operative. Therefore, it functions without hindrance on an intestine devoid of inhibitory control. Consequently, the effect of stimulation of the vagus under these circumstances is maximal. As a rule, the reaction of the blood pressure to vagus stimulation seems to be unaltered by spinal analgesia, and this is in distinct contrast to what we have previously observed in the case of splanchnic analgesia. In splanchnic analgesia, the blood pressure effect following stimulation of the vagus is characteristically abolished, or at least tends to be diminished, presumably owing to diffusion of the solution used in splanchnic analgesia in such a way as to involve at least a part of the plexus cardiacus. Occasionally, as the result of splanchnic analgesia, the effect of the vagus on one side shows diminution or absence, while on the other side little effect can be noted. This lack of uniformity may be dependent either on the position of the animal during and subsequent to the administration of splanchnic block or on anatomic factors as yet undetermined. The reason why the vagus is unaffected in spinal analgesia, in contrast to splanchnic analgesia, is that ordinarily the diffusion of the anesthetic solution is not high enough in the latter to affect the vagus center.

COMMENT

We believe that the use of nicotine in the treatment for intestinal obstruction is contraindicated not only because it is inefficient in increasing intestinal movement, but because of its undesirable blood pressure raising characteristics. Amounts of nicotine sufficient to produce even noticeable splanchnic effects are capable of doubling the blood pressure. Doubling the blood pressure of certain persons clinically, especially those of advanced age and those suffering from cardiovascular disease, would be a hazardous procedure. The use of this drug is definitely contra-

indicated also in view of the fact that we have a better method of blocking the splanchnic nerves, which avoids this undesirable blood pressure change, namely, splanchnic analgesia obtained with procaine hydrochloride. In several cases in this series of experiments, the animals died during the subsequent rapid fall in blood pressure following the initial rise due to nicotine. At first it was considered that the animals died as a result of nicotine poisoning, but in view of the experimental use of the much larger doses of nicotine by Rosenstein and Köhler [1] without fatal results, in the case of rabbits, we were forced to look further for the cause of death. We then discovered that the mechanics involved in the recording of the blood pressure tracing in our experiments were such that considerable quantities of 2 per cent solution of sodium citrate found their way almost directly into the heart of the animal during the period of rapid diminution of blood pressure. As we have been able to produce the death of animals by the rapid introduction of sufficient quantities of 2 per cent solution of sodium citrate directly into the cardiac chambers, we assume that such an occurrence explains our fatalities.

Chemical section of the splanchnic nerves, either by subarachnoid block or by an infiltration of the retroperitoneal space in the region of the splanchnic nerves, as a therapeutic measure, is open to criticism because of the fall of blood pressure which it produces. Depression of the blood pressure is more marked in spinal analgesia than in splanchnic analgesia, and for this reason spinal analgesia is probably less desirable. A decrease in blood pressure is undesirable, because patients suffering from ileus usually have a relatively low blood pressure initially. Any additional decrease in blood pressure is liable to reduce it to unsafe limits. Again we wish to emphasize the fact that the common practice of combating this fall in blood pressure with epinephrine and ephedrine, while highly desirable in spinal injection intended primarily for analgesic effect, seriously minimizes the action of spinal and splanchnic analgesia on intestinal movements (fig. 14). The decrease in effect on the intestines is probably due to a sympathetic stimulation at the neuromuscular junction peripheral to the block produced by the anesthetic solution. As the splanchnic nerves are inhibitory, stimulation of them produces inhibition with resultant loss of tone and cessation of intestinal movements. This is in accord with our experimental observation in that the animals which had previously received these drugs never showed the characteristic intestinal motor effects, and in cases in which motor activity was present, the injection of these drugs speedily caused an inhibition of movements.

Considering the effect of spinal and splanchnic analgesia on motor activity, our evidence seems to show conclusively that splanchnic analgesia is preferable. The reason why splanchnic analgesia is more

efficient than spinal analgesia is by no means apparent, since both procedures involve chemical section of the splanchnic nerves. The difference in effect is apparently dependent on the level at which the block is performed. We provisionally assume that the effect on intestinal tone is more marked following splanchnic analgesia than following spinal analgesia, because not all the pathways of the reflex arc involved in the inhibitory control of tone and intestinal movement pass through the anesthetized part of the cord, but that a part of the mechanism may involve the transmission of impulses through the sympathetic plexuses extradurally, in which case the effect of direct infiltration of the ganglia and plexuses formed by the greater and lesser splanchnic nerves would produce a complete block, whereas subarachnoid block would produce an incomplete one.

Several investigators, notably Domenech,[14] have assumed that intestinal paralysis in peritonitis is due to a reflex involving a sensorimotor arc through the splanchnic nerves. Domenech has shown that paralysis of the splanchnic nerves suffices to overcome the paralysis due to peritonitis. Wagner [15] was able to combat peritonitic ileus by the intraspinal injection of procaine hydrochloride. Apparently these authors have taken for granted that all nerve fibers entering into the formation of this arc pass through the cord. This we do not believe to be necessarily true, since the sympathetic system shows local autonomy and, while connected with the central nervous system, can function independently of it. Both clinically and experimentally the effects of spinal and splanchnic analgesia are subject to considerable variation. These variations are probably due to faults in technic. Such variations are more likely to occur in connection with splanchnic analgesia, due not only to anatomic variations in the position of the sympathetic ganglia, but also to the technical difficulty of the procedure.

In spinal analgesia, while the aspiration of cerbrospinal fluid through the needle is positive evidence that the subarachnoid space has been entered, the point of the needle may not always be maintained within the subarachnoid space during the entire period of the injection of the anesthetic agent, and, moreover, the level to which the analgesia may be obtained is beyond the absolute control of the operator.

CONCLUSIONS

Obviously, splanchnic analgesia will be ineffective in the treatment for ileus in those cases of mechanical intestinal obstruction in which the obstruction has not been previously relieved by surgical intervention. Splanchnic analgesia is a method which should be used early and not as a last resort, since it can hardly be expected that a patient who has already absorbed a lethal dose of toxin can be revived by any means.

The accessory supportive treatment of patients with ileus should not be neglected, especially the treatment for associated alkalosis, dehydration and chloride deficiency.

As experimental splanchnic analgesia produces no marked motor effect on the large intestine, we believe that in the patients treated by such analgesia the insertion of a rectal tube and the administration of an enema, in conjunction with the induction of the splanchnic analgesia, will probably be of value. In the late case, especially in the case of mechanical obstruction, at least one enterostomy should be performed prior to the induction of the splanchnic analgesia.

In those cases of peritonitis in which the peritonitic process tends to be localized, splanchnic analgesia should be used cautiously and only after due consideration, because of the danger of converting a localized into a generalized process.

While the technic of splanchnic analgesia is not particularly difficult, only one who has performed the procedure under close supervision or who has taken occasion to practice the technic on the cadaver and who is thoroughly familiar with the anatomy involved should be considered competent to perform it clinically.

Of the three general methods which have been devised for the production of splanchnic analgesia, the Wendlung technic, which involves puncture of the intact anterior abdominal wall, probably has no place in rational surgical intervention. The Braun technic involves preliminary laparotomy and somewhat extensive intra-abdominal manipulation, and is therefore practically never indicated in the treatment for ileus. The third method, the method of Kappis, which involves the introduction of a needle posteriorly through the flank, is almost invariably the method of choice in the treatment for ileus.

We recommend the use of four points of injection, as originally described by Kappis; one on either side of the midline approximately opposite the first lumbar vertebra, and one on either side below and at corresponding points opposite the second lumbar vertebra. The solution which we use and recommend is a plain 2 per cent solution of procaine hydrochloride in physiologic sodium chloride solution. Twenty cubic centimeters of the solution should be injected at each of the four points. Due to the inhibitory effect of epinephrine, ephedrine and atropine on intestinal movements, these drugs should never be used either before, with, or after splanchnic analgesia when used in the treatment for ileus.

Experimental evidence is conclusive that when nicotine is injected into the splanchnic area it is of little value in increasing intestinal movement, and is also distinctly dangerous because of its marked cardiovascular effects.

Although we have not used spinal analgesia in the treatment for ileus clinically, our experimental results indicate that splanchnic analgesia is preferable to spinal analgesia in increasing intestinal movement; increase in tone is especially noticeable.

Blood pressure determinations should be made both before and after the introduction of an anesthetic solution into the splanchnic area, since a fall in blood pressure is invariably found after successful splanchnic blocks. This decrease in blood pressure indicates that a successful analgesia has probably resulted. While a decrease in blood pressure is theoretically undesirable, we do not believe that it ordinarily constitutes a contraindication to the use of the method as this effect is neither unduly profound nor prolonged. However, it must be admitted that reduction in blood pressure is ordinarily undesirable, and this consideration should not be minimized. It constitutes one of the chief objections to spinal analgesia, in which method blood pressure decreases are characteristically of greater magnitude.

Since the effect of splanchnic analgesia on the motility of the intestine is only transitory (lasting from six to thirty minutes in experimental animals), this procedure may be repeated in case the previous injection has not proved althogether successful after the lapse of as short a time as one hour.

At the risk of repetition, we wish to express ourselves as of the opinion that additional stimulation of the colon, by means of an enema, may be of distinct value as an accessory to the induction of splanchnic analgesia, because of its stimulating effects on colonic movement, the colon being a part of the intestinal tract which is affected only slightly, if at all, by the chemical section of the splanchnic nerves.

Our clinical observations in general surgical practice indicate that intestinal motility is much more frequently noted following splanchnic analgesia than following the induction of spinal analgesia, in spite of the fact that epinephrine has been used more frequently in the former method than in the latter method.

INFLAMMATORY CECAL TUMORS

DIAGNOSIS OF TYPES OF OBSCURE ETIOLOGY *

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Studies of the pathologic enlargements of the ileocecal region usually have been confined to the commoner conditions; for example, neoplasms, tuberculosis and other granulomatous processes of definite etiology. Difficulty usually does not arise in establishing the identity of a malignant condition of the cecum. Earlier diagnosis of these lesions is desirable, however. Similarly, the inflammatory swellings of definite etiology, especially tuberculosis and actinomycosis, usually are readily recognized. But there remains a conspicuous absence of early diagnostic signs.

A brief review of some of the less common cecal tumefactions seems advisable before our series of cases is presented.

Lymphomas occur fairly commonly, but in comparison to carcinomas they are rare lesions. Cinaglia [1] considered lymphomas in considerable detail. The closely allied condition lymphosarcoma was recently reviewed by Rankin and Chumley.[2]

Cholesteatoma is one of the rarest of the cecal tumors. Humiston and Piette [3] reported a case in 1921, and Klemptner and Palmissand [4] another in 1927. The latter was in a girl, aged 18, and the tumor was found in the course of operation for ruptured appendix. A glistening tumor, 7.5 by 0.5 cm., was peeled out of the wall of the cecum. They concluded that the origin of the cholesteatoma probably was an embryonic displacement of epidermal cells.

Lipoma of the cecum, like most of these lesions, has been identified only at operation. Comfort [5] recently reported twenty-eight cases.

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* From the Division of Medicine, the Mayo Clinic.

1. Cinaglia, Raniero: Linfoma dell'intestino cieco, Policlinico **33**:1085, 1926.

2. Rankin, F. W., and Chumley, C. L.: Lymphosarcoma of the Colon and Rectum, Minnesota Med. **12**:247, 1929.

3. Humiston, C. E., and Piette, E. C.: True Cholesteatoma of the Cecum, J. A. M. A. **84**:874 (March 21) 1925.

4. Klemptner, Dietrich; and Palmissand, D. J.: Cholesteatoma of Cecum, Illinois M. J. **52**:82, 1927.

5. Comfort, M. W.: Submucous Lipomas of the Gastro-Intestinal Tract, to be published.

Matry [6] reported a case in which intussusception resulted. The preoperative diagnosis in these cases has usually been polyp. Although single polyps occur in the cecum, they are usually a part of a general polyposis of the colon.

Leiomyoma of the cecum has been described, and Podlaha [7] found a large one on the posterior wall of the cecum in a patient who was in good general condition.

Bazin [8] reported a congenital mucous cyst in a child 8 months of age.

Pendl [9] expressed the belief that hemorrhagic infarction of the cecum, with tumor formation, is caused by embolism or thrombosis of the superior mesenteric artery.

The "mobile cecum" or "pelvic cecum" associated with extreme and habitual constipation is apparently a source of trouble. Schmieden [10] expressed the opinion that the best treatment for this is resection. There are numerous inflammatory conditions in this region which often cause serious trouble and much diagnostic difficulty.

Although diverticulosis and diverticulitis of the right side of the colon are usually only a part of a condition of diverticulosis of the large intestine, instances of cecal diverticulitis without diverticulosis of the remainder of the colon have been noted. Cooke,[11] French [12] and Greensfelder and Hiller [13] called attention to the rarity of such a condition. The latter reported four cases of traumatic solitary diverticula, 2 found in the course of 5,385 major operations and 2 in 400 necropsies on adults at the Michael Reese Hospital of Chicago.

There is another and a more common pericecal and cecal inflammatory lesion, with the formation of tumor, which at times causes obstruction, and the etiology of this is even more uncertain than that of some of those noted. W. J. Mayo,[14] in 1888, reported cases in which typhlitis or perityphlitis gave rise to palpable tumors. Similar conditions

6. Matry, C.: Lipome du caecum. Invagination. Colectomie droite. Guérison, Bull. et mém. Soc. nat. de chir. **54**:1375, 1928.

7. Podlaha, J.: Leiomyoma of the Cecum, Čas. lék. česk. **63**:1585, 1924.

8. Bazin, A. I.: Mucous Cyst of Caecum (Congenital); Primary Intussusception: General Considerations, Canad. M. A. J. **15**:130, 1925.

9. Pendl, Fritz: Hämorrhagischer Infarkt des Coecum, Beitr. z. klin. Chir. **145**:606, 1929.

10. Schmieden: The Mobile Cecum as a Cause of Disease, Berlin Letter, J. A. M. A. **93**:135 (July 13) 1929.

11. Cooke, A. B.: When Appendicitis Is Not Appendicitis; A Case of Diverticulitis of the Cecum, J. A. M. A. **78**:578 (Feb. 25) 1922.

12. French, R. W.: Diverticulitis of the Cecum with Report of Three Cases, Boston M. & S. J. **189**:307, 1923.

13. Greensfelder, L. A., and Hiller, R. I.: Cecal Diverticulosis with Special Reference to Traumatic Diverticula, Surg. Gynec. Obst. **48**:786, 1929.

14. Mayo, W. J.: Inflammations Involving the Cecum, Its Appendix, or Both, Tr. Minnesota State Med. Soc., 1888, p. 63.

have since been noted repeatedly. Rankin [15] published illustrations and a description of this condition. Hartwell,[16] in 1921, and Kolouch,[17] in 1923, spoke of nontuberculous inflammations of the cecum. Bachlechner [18] stated that recurrent chronic appendicitis caused these lesions. Lazarus [19] reported five cases of primary inflammatory tumors of the cecum without involvement of the appendix. He considered trauma, infection and decubitus ulceration as factors in their etiology. He made note of the fact that ileocolostomy and resection may become necessary because of inability to make a diagnosis without removing the ileocecal portion of the bowel. Walters and Synhorst [20] called attention to the "ligneous infection" of the cecum. Erdmann and Clark,[21] in a report of forty-eight cases in which tumors of the cecum occurred, noted that thirty-seven were caused by carcinoma, seven by tuberculosis, two by lymphosarcoma and two by chronic inflammation of undetermined etiology. Nemilov [22] called attention to the fact that these tumors may arise after appendectomy; he expressed the belief that the silk ligature used to invert the appendiceal stump may be their point of origin. He regretted the fact that neither textbooks nor surgical monographs call attention to this condition. It was this relative rareness, the accompanying diagnostic difficulties and the therapeutic problems that these inflammatory tumors presented which led us to report this series of cases.

The first ten cases which compose group 1 represent inflammatory lesions of the ileocecal coil which caused considerable diagnostic difficulty and which did not present a definite disease entity from the standpoint of etiology.

Group 2 is made up of the next nine cases, which were particularly difficult to distinguish from the cases of group 1. Finally, they proved to be due to well recognized organic disease.

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15. Rankin, F. W.: Surgery of the Colon, New York, D. Appleton & Company, 1926, pp. 366.

16. Hartwell, J. A.: Non-Tubercular Inflammation of Cecum, S. Clin. N. Amer. **1**:361, 1921.

17. Kolouch, F. G.: Non-Tuberculous Inflammation of Cecum, Nebraska M. J. **8**:106, 1923.

18. Bachlechner, Karl: Ueber entzündliche Ileocecaltumoren, Beitr. z. klin. Chir. **124**:103, 1921.

19. Lazarus, J. A.: Primary Inflammatory Tumor of the Cecum Without Appendicitis, Am. J. Surg. **1**:350, 1926.

20. Walters, Waltman; and Synhorst, A. P.: Ligneous Infection of Cecum Resulting from Subacute Appendicitis, S. Clin. N. Amer. **6**:1203, 1926.

21. Erdmann, J. F., and Clark, H. E.: Tumors of Cecum; Discussion and Report of Forty-Eight Cases, Ann. Surg. **85**:722, 1927.

22. Nemilov, Alexander: Ueber entzündliche Dickdarmgeschwülste und ihre Bedeutung in der Pathologie des Blinddarms, Arch. f. klin. Chir. **43**:346, 1928.

In the last three cases, group 3, the patients had real trouble but at times little was grossly demonstrable. If such cases are carefully chosen, they offer a field for unusual therapeutic results.

REPORT OF CASES

Group 1: Inflammatory Lesions of the Ileocecal Coil Causing Palpable Tumor or Roentgenologic Deformity or Both.—CASE 1.—A farmer, aged 48, came to the clinic in March, 1928, complaining of "a mass in the abdomen." Three weeks before admission he had diarrhea for one day, and two days after that he had an attack of repeated sharp pains due to gas, with much borborygmus which finally had been relieved by enemas. Following this he had been in bed for three days and had lost 10 pounds (4.5 Kg.). Examination by a physician at that time revealed a slightly tender mass in the right lower quadrant of the abdomen. In a week his bowels moved regularly again, and he gained strength and felt well. At no time had any blood been seen in the stools, and he did not know that he had had fever.

General examination on admission revealed nothing of note except a mass about 8 cm. in diameter, slightly tender and fixed, in the right lower quadrant of the abdomen. The temperature was 98.4 F. Movements of the bowels were regular about the time he was admitted. The concentration of hemoglobin was estimated at 72 per cent; erythrocytes numbered 4,200,000 and leukocytes, 4,600 for each cubic millimeter of blood. Roentgenologic examination of the colon after a barium enema revealed deformity of the cecum in a portion corresponding to that of the palpable mass. Roentgenograms of the thorax gave negative results. There were no parasites or ova in the stools examined, and no occult blood was found. A probable diagnosis of malignant lesion of the cecum was made.

Exploration was undertaken, and ileocolostomy was done. Investigation of the lesion, with the abdomen open, suggested the surgical diagnosis of carcinoma of the cecum. Resection of the right side of the colon was undertaken later, and the pathologic report on the specimen removed was as follows: "Mucosa intact; stricture due to a chronic abscess in the walls of the ileum and cecum. No carcinoma found" (figs. 1, 2 and 3).

The excellent general condition of the patient and the short history were distinctly against the diagnosis of a malignant condition. Nevertheless, the mass and deformity of the cecum placed malignancy uppermost in our minds and demanded exploration.

CASE 2.—A single woman, aged 28, came to the clinic on Feb. 23, 1928, because of a lump in the lower right quadrant of the abdomen. In 1921, she had an appendectomy performed elsewhere than at the clinic. In 1922, she had begun to have burning discomfort across the upper part of the abdomen, with nausea. In 1926, a burning, aching type of pain had begun, with cramps about the umbilicus and in the right lower quadrant of the abdomen; these attacks had lasted for one or two days and had occurred at frequent intervals, occasionally associated with vomiting, fever and bloating. In November, 1926, exploration had been undertaken elsewhere, and the following report had been given: "Much straw-colored fluid found in the abdomen and a lump the size of a hen's egg in the right lower quadrant; a specimen removed failed to show tuberculosis or malignancy." After the exploration, the lump had increased in size, and after

roentgenologic examination the lumen of the cecum had been reported as becoming smaller. There had been no loss of weight.

On the patient's admission to the clinic, there was a movable, tender mass in the right lower quadrant of the abdomen. There was no clinical evidence of thoracic disease, but roentgenograms showed evidence of scars in both apexes, as of an old tuberculous process. On one occasion the temperature was 99.6 F. Concentration of hemoglobin was estimated at 71 per cent; erythrocytes numbered 4,600,000 and leukocytes, 6,200 in each cubic millimeter of blood. On February 24, roentgenologic examination of the colon after a barium enema disclosed a filling

Fig. 1.—Colon after barium enema, presenting smooth angular deformity of the cecum.

defect in the cecum and ascending colon, and another roentgenologic examination, on March 14, suggested that the lesion was extrinsic to the cecum.

On March 20, exploration was undertaken, ileocolostomy was done and an indeterminate diagnosis of cecal mass was made. On April 5, resection of the right side of the colon was done, and a diagnosis was made on the basis of pathologic evidence of chronic inflammatory lesion and contraction of the lumen (figs. 4 and 5).

The long history of the lesion of the right lower quadrant of the abdomen, the history of the finding of straw-colored fluid in the abdomen

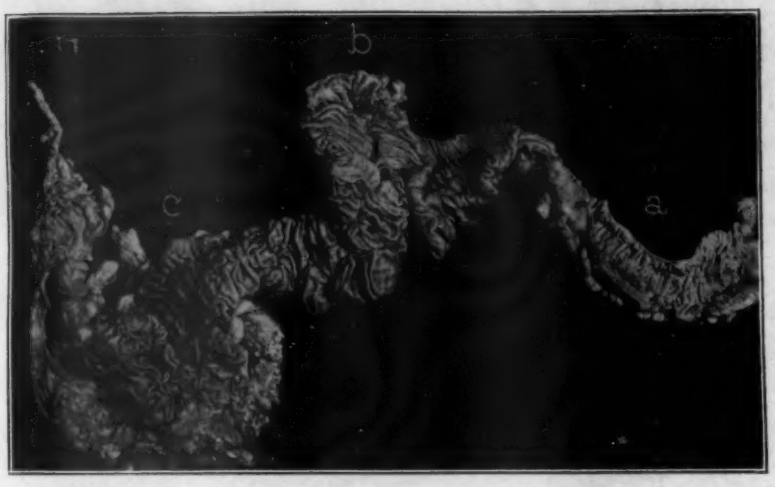

Fig. 2.—Cecum, ascending colon and terminal portion of the ileum opened to show the mucosa after resection; *a*, ileum; *b*, cecum; *c*, ascending colon.

Fig. 3.—Lateral view of the cecum with section through the lesion; *a*, ileum; *b*, cecum; *c*, ascending colon.

at previous exploration and the disclosure by roentgenogram of the thorax of an old, healed tuberculous lesion demanded, in spite of the negative result of the biopsy which was done elsewhere, that tuberculosis be considered. In spite of the fact that our exploration revealed only a chronic ulcerative, inflammatory lesion, it still is doubtful that we have ruled out tuberculosis in this case.

CASE 3.—A man, aged 43, came to the clinic on Oct 8, 1929. He had undergone appendectomy elsewhere than at the clinic in November, 1928. For a month

Fig. 4.—Colon after barium enema, presenting the large defect thought to be due to a pericecal lesion.

preceding this there had been recurrent attacks of abdominal distress, diffuse at first, but eventually localized more on the right side. Two weeks after the appendectomy, he had begun to have diarrhea and had averaged between five and six loose, watery stools in twenty-four hours. In June, 1929, the diarrhea had become more severe, so that he was having between twelve and eighteen loose stools, with much cramping and pain in the lower part of the abdomen. The stools had been liquid and black. Fresh blood had not been seen. There had been nausea and vomiting. In August, an abscess formed in the scar that followed appendectomy. After this abscess had formed, it had opened and closed at intervals. Six weeks before admission, the patient had lost weight and strength rapidly. His weight in health had been 170 pounds (77.1 Kg.).

Examination on the patient's admission to the clinic revealed that he weighed 138 pounds (62.6 Kg.). He appeared to be anemic and was markedly weak. There was generalized anasarca, graded 3, in the legs and in the arms. The hemoglobin at this time was estimated at 40 per cent; erythrocytes numbered 2,010,000 for each cubic millimeter of blood. There was a firm, apparently fixed mass in the right lower quadrant of the abdomen, just to the right of the old operative scar. Roentgenologic examination of the colon showed evidence of an ulcerative lesion of the ascending and transverse colon. Roentgenograms of the thorax revealed healed lesions in both apexes, and there were no clinical signs

Fig. 5.—Resected specimen opened to show the mucosa; *a*, tip of cecum; *b*, ascending colon.

of thoracic disease. The diagnosis rested between tuberculosis and chronic ulcerative colitis. The patient's condition made it inadvisable to consider surgical intervention. Measures for general upbuilding, relief from edema and transfusions were instituted, and although there was temporary improvement, the patient died on November 2. Necropsy revealed a healing ulcerative lesion of the ascending and transverse colon, a dense, fibrous stricture at the ileocecal valve and polyposis of the ascending colon (figs. 6 and 7).

Any ulcerative lesion of the right side of the colon should cause tuberculosis and chronic ulcerative colitis to be included in the differen-

tial diagnosis. The roentgenologic observation of old pulmonary tuberculosis and the presence of the mass in the right lower quadrant of the abdomen indicated tuberculosis in this case. However, the absence of activity in the thorax and the absence of acid-fast bacilli in ten successive examinations of stools and sputum were decidedly against the diagnosis of tuberculosis. Necropsy disclosed chronic ulcerative colitis and polyposis. The latter is a complication that occurs in about 10 per

Fig. 6.—Colon after barium enema, showing the ulcerative lesion of the ascending and transverse colon and the stoppage of barium at the cecum.

cent of cases of chronic ulcerative colitis. The stricture of the ileocecal region has not been explained, but the effect of a foreign body must be considered in its causation.

CASE 4.—A man, aged 36, came to the clinic on June 21, 1927, complaining of pain in the right lower quadrant of the abdomen. He said that two years before coming to the clinic his trouble had begun with cramps in the lower part of the abdomen, nausea, fever and vomiting, followed by residual soreness. In March, appendectomy without drainage had been done, followed by fever for five days, and since that time aching in this region had been continuous and had

projected toward the right hip. One month before the patient came to the clinic abdominal cramps had been worse than before and had been increased in severity by exercise, and by taking food and drink. Three weeks before he was admitted he had begun to pass watery, lumpy stools. About that time, he first noticed the mass in the right lower quadrant of the abdomen.

On the patient's admission to the clinic, except for a hard, seemingly fixed mass in the right lower quadrant of the abdomen, the results of general examination were inconsequential. The concentration of hemoglobin was estimated at 75 per cent by the Dare method; erythrocytes numbered 4,970,000 and leukocytes, 9,100 in each cubic millimeter of blood; 35 per cent of the leukocytes were lymphocytes. Roentgenologic examination of the colon after a barium enema gave a suggestion of a filling defect. The temperature was 99 F. on one occasion. There was a loss of weight of 10 pounds (4.5 Kg.). A diagnosis of cecal tumor

Fig. 7.—Specimen removed at necropsy viewed from the mucosal side; *a*, ileum; *b*, stricture; *c*, ascending colon with polyps.

(carcinoma or inflammatory) was made. Exploration revealed an inflammatory tumor at McBurney's point in the abdominal wall, to which the cecum was adherent. A specimen was removed.

The shortness of the history, the sudden onset of the condition and the normal blood picture in this case were against the diagnosis of a malignant condition. The mass and the filling defect brought such a condition into consideration in the differential diagnosis.

Case 5.—A man, aged 53, came to the clinic on Oct. 11, 1926, complaining of intermittent pain of ten years' duration in the lower part of the abdomen. The pain usually started suddenly with cramps, was worse when the patient was lying down and was relieved by voiding, enemas and purging.

Except for the mass in the right lower quadrant of the abdomen, which was firm and was apparently fixed and tender, the general examination gave negative results. The concentration of hemoglobin was estimated as 76 per cent. There were 4,580,000 erythrocytes and 8,700 leukocytes in each cubic millimeter of blood. Roentgenologic examination of the colon after a barium enema disclosed a filling defect of the cecum. A diagnosis of a lesion of the cecum was made, and at exploration a diagnosis of malignant growth of the cecum. Ileocolostomy was done. Three weeks later, a second operation was done with the intention of resecting the growth. This time it was discovered that the mass had almost disappeared; it was found to be due to an appendical abscess (fig. 8).

Fig. 8.—Colon after barium enema, presenting smooth angular deformity of the cecum (similar to that of fig. 1).

The difficulty of diagnosing these lesions is illustrated in this case. Roentgenologic examination revealed a definite filling defect. The surgeon who saw the lesion thought that it was a carcinoma. A second exploration was necessary to make the diagnosis of appendical abscess.

CASE 6.—A boy, aged 6 years, was brought to the clinic on March 1, 1926, with a history of intestinal trouble of five years' duration. There was a history of diarrhea, beginning at the age of 10 months, of anorexia and of blood and mucus in the stools. Attacks were becoming more frequent and more severe. At no time had there been more than five or six stools in twenty-four hours.

The patient was a fairly well nourished boy, small for his age. He was 7 pounds (3.2 Kg.) underweight. The temperature was 99 F. on one occasion. The concentration of hemoglobin was 75 per cent; erythrocytes numbered 5,000,000, and leukocytes, 7,100 in each cubic millimeter of blood. Sigmoiditis was found on proctoscopic examination, and cultures made from the lesion revealed the usual diplostreptococcus that is found in cases of chronic ulcerative colitis. Roentgenologic examination after a barium enema showed a lesion of the cecum and ascending colon and a filling defect of the cecum. A diagnosis of chronic ulcerative colitis and pericecal abscess was made.

The age of the patient, the presence of chronic ulcerative colitis and the mildness of the symptoms were against the filling defect being due to a malignant lesion. With the absence of obstructive symptoms, it seemed wise to treat the patient by medical means. A letter in October, 1929, reported that he was free from symptoms of disease of the large intestine three and a half years later.

CASE 7.—A woman, aged 56, came to the clinic because of pain in the abdomen of five months' duration. The pain usually began about the umbilicus and spread to both lower quadrants and to the back, and sometimes to the left shoulder; it occurred about every ten days and lasted for several days. In the three weeks before admission to the clinic, the attacks had become frequent. There had been three severe spells, with vomiting and residual soreness. Voiding of urine was increased with the attacks.

Examination revealed a tender hard mass in the right lower quadrant of the abdomen and nothing else of note. There was a loss of weight of 4 pounds (1.8 Kg.). The concentration of hemoglobin was estimated as 63 per cent; erythrocytes numbered 3,890,000 and leukocytes, 6,700 in each cubic millimeter of blood. Roentgenologic examination after a barium enema was unsatisfactory, but gave evidence of a possible lesion of the cecum. Diagnosis of tumor of the cecum was made, and at exploration a ligneous infection and subacute appendicitis were found. The appendix was removed.

The size of the tumor, the duration of the disease, the obstructive attacks from the cecal lesion and their severity would suggest inflammatory disease as the cause of the symptoms in this case.

CASE 8.—A man, aged 64, came to the clinic on July 13, 1926, with a history of slight intermittent pain and soreness in the right lower quadrant of three weeks' duration. He had lost 30 pounds (13.6 Kg.) in six months. He had mild diabetes.

There was a small, tender, movable mass in the right lower quadrant of the abdomen; nothing else of note was found on general examination, except marked arteriosclerosis. The concentration of hemoglobin was estimated at 73 per cent; erythrocytes numbered 5,350,000 and leukocytes, 5,600 in each cubic millimeter of blood. Roentgenologic examination following a barium enema gave evidence of slight deformity of the cecum. A diagnosis of chronic appendicitis was made. Exploration revealed subacute intestinal obstruction from adhesions about the lower part of the ileum. The adhesions were freed. It was thought that they might have caused the tumor. Because of the marked arteriosclerosis the question of a small infarct as the basis of the condition was considered.

In spite of the patient's age, the palpable tumor and the loss of weight, it would hardly seem probable that a malignant lesion would be found in this case. Exploration, with a resulting diagnosis of inflammatory disease, settled the question.

CASE 9.—A woman, aged 53, came to the clinic on Feb. 10, 1926, with a history of recurrent attacks of abdominal distress, progressively increasing difficulty in moving the bowels, small stools and much borborygmus. She had had this trouble for eleven years, but had not lost weight. There seemed to be a tender mass in the region of the ascending colon.

Roentgenologic examination following a barium enema gave evidence of a lesion of the cecum and ascending colon, with a stricture at the hepatic flexure. The temperature was normal. The concentration of hemoglobin was estimated at 74 per cent. Leukocytes numbered 8,100. A diagnosis of malignant lesion of the ascending colon was made. Exploration revealed a stricture at the juncture of the cecum and ascending colon. The stricture was excised, and a plastic operation and ileocolostomy were done.

The size of the lesion and the recent increase of trouble, as well as the deformity revealed in roentgenologic examination, caused us to consider a malignant process as the etiologic factor in this case.

CASE 10.—A man, aged 67, came to the clinic on Dec. 19, 1928, with a history of having had intermittent diarrhea for twenty years. He had had attacks of cramping pain in the right lower quadrant and a feeling that "stoppage" to gas and feces was taking place. The severity of the pain had increased. Analysis of gastric content done elsewhere than at the clinic showed that free hydrochloric acid was absent. Hydrochloric acid taken during the six weeks before admission had caused improvement in the attacks of diarrhea, but they had continued intermittently. He had lost 30 pounds (13.6 Kg.) in the six months prior to his coming to the clinic.

The concentration of hemoglobin was estimated at 66 per cent; erythrocytes numbered 3,350,000 and leukocytes, 6,300 in each cubic millimeter of blood. There was marked tremor of the head and body. In consultation with the neurologist, we noted early changes in the spinal cord, and the presence of combined sclerosis was considered. Analysis of gastric content after a test meal did not reveal free hydrochloric acid. Roentgenologic examination of the colon after a barium enema showed a spastic filling defect in the cecum, probably due to tuberculosis. Roentgenograms of the thorax gave negative results. A diagnosis of tumor of the cecum was made, and exploration was undertaken. A large, boggy cecum, deformed by marked adhesions between the parietal and visceral peritoneum on the right side and a chronically inflamed appendix were found. The adhesions were freed and appendectomy was done. Subsequent treatment for the anemia was instituted.

The age of the patient, the anemia and the intermittent diarrhea pointed to a lesion of the cecum. The anemia, the high color index and the early changes in the spinal cord, however, could explain the picture, except the cecal deformity, on a basis of pernicious anemia.

Group 2: Definite Pathologic Conditions That Are Difficult to Differentiate from Those of Group 1.—CASE 11.—A man, aged 41, came to the clinic on Dec.

16, 1927, complaining of "stomach trouble" of four years' duration. This had occurred as irregular attacks of pain and tenderness in the right lower quadrant of the abdomen. The attacks had become more severe in the year before he came to the clinic. They had occurred several hours after meals and at about 10 p. m. At times a sausage-shaped tumor had appeared beneath the scar following appendectomy which had been done elsewhere in 1925. There was a history of epididymitis.

Examination revealed a tender "ballooned" region in the right lower quadrant of the abdomen. The patient had lost 35 pounds (15.9 Kg.) in four years. Hemoglobin was in a concentration of 65 per cent; erythrocytes numbered 4,390,000 and leukocytes, 17,300 in each cubic millimeter of blood. Roentgenologic examination of the colon after barium enema gave negative results. A diagnosis of a cecal lesion, with obstruction, was made. Exploration revealed a tumor, which appeared to be inflammatory, extending from the ileocecal juncture to the hepatic flexure. It was so large, and there was so much inflammation about it, that removal was not possible. Ileocolostomy was done.

The patient returned home and made some general improvement, but five months after the first operation trouble reappeared. He returned to the clinic. Exploration at this time showed that the tumor was much larger, and the surgeon considered tuberculosis and a malignant process as possible factors in its causation. He did not attempt to remove it, because if it were tuberculous its removal would be associated with too great a risk, and if malignant, it was clearly inoperable. The postoperative recovery was uneventful, and the patient returned home. It was reported several months later that he had died and that adenocarcinoma had been discovered at necropsy.

This case illustrates well the difficulty encountered in making a diagnosis of some of these cecal lesions. There was a huge tumor without evident defect in the roentgenogram, a slight degree of anemia and a fair general condition. At exploration so much secondary infection was found that a diagnosis could not be established.

CASE 12.—A man, aged 48, came to the clinic on Aug. 29, 1926, complaining of attacks of abdominal pain of nine years' duration. The attacks usually had started as "twinges" of abdominal pain, increasing to sharp "squeezing" pain which doubled him up. Pains occurred from every three to four minutes and lasted for about one minute. At the end of five or six hours of such an attack, he would vomit. Morphine sulphate had been required for relief. He had had these attacks as often as three or four times in two weeks, and sometimes had been free from them for two or three months at a time.

The temperature was not elevated. Hemoglobin was in a concentration of 74 per cent; erythrocytes numbered 4,430,000 and leukocytes, 5,000 in each cubic millimeter of blood. Roentgenologic examination of the colon after a barium enema gave evidence of a deformity of the cecum that was thought to be the result of an old inflammatory or congenital lesion. Roentgenograms of the thorax showed signs of an old bilateral pulmonary tuberculous process. Clinically, the nature of the cecal lesion was not established. Exploration revealed three hyperplastic, obstructing, tuberculous lesions: one of the cecum and two of the lower part of the ileum. These lesions caused stricture of the intestine, and ileo-ileostomy and ileocolostomy were done, which short-circuited about 90 cm. of the ileum. On account of the extent of the lesion, resection did not seem advisable. Recovery was uneventful, and the patient returned two years later in a good general condition.

This case illustrates clearly how extensive hyperplastic tuberculosis can be without producing much trouble as long as obstruction is relieved.

CASE 13.—A man, aged 46, came to the clinic in 1923 because of chronic ulcerative colitis.[23] His trouble was mild, and irrigations with medicated solutions were advised. He got along fairly well; he had between five and six loose stools daily, frequently mixed with blood. In October, 1926, he began to have pain in the right lower quadrant, which was noted particularly before movement of the bowels. About December 20, after he had carried a full sack of wheat to the top of his granary, he experienced a severe, sudden pain in the lower right part of the abdomen, followed by fever, nausea and vomiting. Several days after that, he noticed a mass in the region in which he had had the pain.

The patient came to the clinic again on Jan. 5, 1927, at which time he was having about six rectal discharges every twenty-four hours, mixed with blood and pus, and had a rather tender mass below McBurney's point. His temperature was 99 F. He had lost 17 pounds (7.7 Kg.) in the two months previous to admission. The concentration of hemoglobin was estimated at 57 per cent; erythrocytes numbered 3,560,000 and leukocytes, 12,100 in each cubic millimeter of blood. Roentgenologic examination of the colon after a barium enema showed evidence of a filling defect of the cecum and the deformity of chronic ulcerative colitis. A diagnosis of chronic ulcerative colitis and cecal tumor was made. Exploration revealed a tumor of the cecum that was thought to be malignant, but the tissues around it were the site of much inflammatory reaction. Ileocolostomy was done on January 21. After a stormy course, the patient was discharged from the hospital and returned home. He came back early in March, and his condition had improved to such an extent that on March 16 resection of the tumor, a huge lymphosarcoma, was done. The patient again experienced a stormy convalescence and finally returned home. About a month before this report was completed, a report showed him to be in fairly good health and back at work on his farm.

Because of the presence of chronic ulcerative colitis, the sudden onset of the attack of pain and the circumstances under which it occurred, our first consideration was perforation of the cecum with abscess formation. The size of the tumor, its mobility and the question of obstruction, however, made exploration advisable.

CASE 14.—A woman, aged 43, came to the clinic on Nov. 30, 1928, complaining of cramping epigastric pain, with much rumbling. The condition had been present for several years, but the attacks had increased in frequency and severity in the last few months. She had lost 10 pounds (4.5 Kg.). Examination revealed a mass in the right side of the abdomen which could be pushed up and down and from side to side. Hemoglobin was in a concentration of 74 per cent. Erythrocytes numbered 4,430,000 and leukocytes, 5,000 in each cubic millimeter of blood. Roentgenologic examination of the stomach and thorax gave negative results. Investigation of the colon by roentgenologic methods, after a barium enema, showed a polypoid filling defect in the distal portion of the ascending colon.

Exploration revealed what was thought to be a polyp of the cecum, and ileocolostomy was performed, and later right hemicolectomy. The pathologist found the lesion to be a pedunculated lipoma.

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23. Bargen, J. A.: Chronic Ulcerative Colitis Associated with Malignant Disease, Arch. Surg. **17**:561 (Oct.) 1928.

The movable mass, the symptoms of obstruction and the good general condition suggested that this lesion was of the polypoid type. In the absence of lipomas elsewhere in the body, it would be difficult even to suspect the nature of such a lesion.

CASE 15.—A man, aged 62, came to the clinic on June 17, 1921, because of pain in the abdomen. One year prior to admission, he had begun to have soreness and cramping pain in the abdomen. It had been generalized over the abdomen and had increased in severity, although it had been worse in the right lower quadrant above a large inguinal hernia. There was also rather marked arteriosclerosis. Four or five months prior to admission, the patient had lost 20 pounds (9 Kg.).

The concentration of hemoglobin was estimated at 64 per cent; erythrocytes numbered 3,560,000 and leukocytes, 5,600 in each cubic millimeter of blood. Roentgenologic examination of the colon after a barium enema gave negative results. It was thought that the large scrotal hernia or adhesions in that region might explain the distress, and the patient was sent to the surgeon for herniotomy. Exploration revealed carcinoma of the cecum. Right herniotomy and resection of the ileocecal coil were performed.

The negative result of the roentgenologic examination of the colon and the presence of the large hernia misled the clinician. The attacks of obstruction, the loss of weight and the anemia would suggest a lesion of bowel. Knowledge of the fact that an occasional "silent" carcinoma of the bowel occurs made exploration advisable here.

CASE 16.—A man, aged 31, came to the clinic on May 20, 1926, because of a mass in the right lower quadrant of the abdomen which he had found accidentally two months prior to his admission. It was enlarging and occasionally he had a dull pain in the abdomen. There had been no change in the regularity of the movements in his bowels. Appendectomy had been performed elsewhere in 1916.

Examination revealed a rather firm, somewhat fixed mass in the right lower quadrant of the abdomen. There had been no loss of weight. The concentration of hemoglobin was 82 per cent; erythrocytes numbered 4,850,000 and leukocytes, 9,400 in each cubic millimeter of blood. The results of roentgenologic examination of the colon after a barium enema were reported as negative; the mass was extrinsic to the colon. The patient was sent to the surgeon with a diagnosis of a tumor in the region of the cecum. Exploration revealed an inoperable carcinoma of the posterior wall of the ascending colon with extensive metastasis in the liver.

This case illustrates the extent to which malignant lesions of the colon may advance before producing clinical signs and symptoms. In this case the roentgenogram of the colon and the blood count were negative and there was no loss of weight, yet a hopelessly inoperable malignant lesion was found.

CASE 17.—A woman, aged 43, a teacher, came to the clinic on June 18, 1928, with multiple complaints, among them weakness. At this time there were no objective symptoms except that she weighed 4 pounds (1.8 Kg.) less than she said she had weighed a year before. Prior to her coming to the clinic she had

undergone appendectomy, hemorrhoidectomy and an operation for strangulated hernia.

The hemoglobin was estimated at 45 per cent, the erythrocytes numbered 2,840,000 and leukocytes, 7,000 in each cubic millimeter of blood; there was some tenderness in the lower part of the abdomen.

The patient was advised at the clinic to go home, adopt general upbuilding measures which were prescribed and to return in two months for further observation, which she did. The pain in the lower part of the abdomen had continued, although there had been improvement in the general condition. She had not had diarrhea. At this time roentgenologic examination of the colon disclosed a filling defect in the tip of the cecum which was thought to be due to a malignant condition. Exploration revealed an inflammatory lesion of the ileocecal coil. This was resected. The pathologist reported a tuberculous condition. There had been no evidence of tuberculosis elsewhere.

This case illustrates the difficulties encountered in diagnosis of localized tuberculosis of the intestine.

CASE 18.—A man, aged 55, came to the clinic on June 20, 1927, complaining of soreness in the right lower quadrant of the abdomen. There had been a "catch" and soreness in the right lower quadrant, associated with a dull ache, for from six to eight months prior to his admission. It often came on from one and a half to three hours after meals and lasted for an hour or so; it was not relieved by the taking of food or sodium. There was considerable borborygmus for six months, although the regularity of the movements of the bowels had not changed. He was told elsewhere that he had a tumor of the right kidney.

In the right lower quadrant, examination revealed a movable mass, which seemed to be lobulated. The concentration of hemoglobin was 64 per cent; erythrocytes numbered 4,360,000 and leukocytes, 11,400 in each cubic millimeter of blood. Roentgenologic examination of the colon after a barium enema disclosed a filling defect of the cecum. A diagnosis of a malignant lesion of the cecum was made, and exploration revealed a carcinoma of the cecum which the pathologist reported as adenocarcinoma.

The only striking feature in this case was the size and mobility of the tumor without any particular symptoms referable to the bowels.

CASE 19.—A man, aged 44, a carpenter, came to the clinic on Dec. 12, 1927, with a story of having had three attacks of pain in the right lower portion of the abdomen, with vomiting in the last two years. The last attack had occurred in January, at which time there had been pain, vomiting and fever. An operation had been done elsewhere, at which time an appendical abscess had been drained. The appendix had not been removed, and a fistula had persisted since the operation. It had been difficult to move the bowels since the time of the operation.

Examination revealed a somewhat undernourished man, who weighed 20 pounds (9 Kg.) less than he said he had been accustomed to weigh. There was a draining sinus in the right lower part of the abdomen, about which there was considerable induration. Examination of the material which drained from the fistula did not reveal sulphur bodies or acid-fast bacilli. The concentration of hemoglobin was estimated at 73 per cent; erythrocytes numbered 4,760,000 and leukocytes, 8,200 in each cubic millimeter of blood. A diagnosis of appendical abscess was made, and exploration revealed colloid carcinoma and a fistula. The pathologist's report was colloid carcinoma with lymphatic involvement.

The history of attacks of pain and of drainage of what seemed to be an appendical abscess, together with the absence of specific inflammatory disease, suggested the diagnosis of appendical abscess with fistula. The increasing difficulty in moving the bowels and the persistent sinus would suggest the advisability of further investigation of the large intestine.

Group 3: Marked Obstipation in Which So-Called Pelvic Cecum Caused Difficulties in the Differential Diagnosis.—CASE 20.—A man, aged 48, came to the clinic on Dec. 16, 1927, complaining of "stomach and bowel trouble" of many years' duration. Constipation had been lifelong. Appendectomy had been done in 1912, without effect on the constipation. For twenty-five years spells had occurred every two or three months and had lasted from one to two hours, in which pain in the epigastrium had come on before breakfast and again at 10 a. m. and at 3 and 8 p. m. These spells had been associated with physical and mental fatigue and depression. After a spell there had been severe muscular pains, especially lumbago, so severe that he had had to go to bed. These spells had been associated with bloating, obstipation, pressure pain in the epigastrium and some tenderness and fever.

Results of examination for organic disease were essentially negative. The concentration of hemoglobin was estimated at 73 per cent; erythrocytes numbered 4,540,000 and leukocytes, 7,600 in each cubic millimeter of blood. A note was made by the clinician of constipation, graded 4. Roentgenograms of the colon after a barium enema were negative, but an examination made to determine the presence or absence of gastro-intestinal stasis revealed a moderate amount of barium in the cecum and transverse colon forty hours after its administration. A diagnosis of intestinal stasis, with partial obstruction, was made. Exploration revealed a large, prolapsed cecum, and ileocolostomy and subsequently right hemicolectomy were performed. The patient has enjoyed normal health since the operation.

CASE 21.—A married woman, aged 40, came to the clinic on Nov. 10, 1927, complaining of enlarging abdomen and pain in the back. She had undergone appendectomy in 1915, and perineorrhaphy in 1926. She had so-called influenza in February, 1927. About July and August, the cramping of muscles and slowly progressive increase in the size of the abdomen were noted. Movements of the bowels had been regular until about a month before admission. Since then, there had been a few spells of mild diarrhea.

Examination revealed a movable mass in the right lower quadrant of the abdomen. The tumor did not seem to be palpable on pelvic examination, and on the following day it could not be palpated in examination of the abdomen. The blood count was within normal limits. Roentgenographic examination of the colon and thorax gave negative results. The possibility of a mesenteric cyst or of a pedunculated ovarian cyst was raised, and exploration was advised. This revealed a redundant, prolapsed cecum lying low in the pelvis, and a modified Waugh operation was done.

CASE 22.—A woman, aged 63, came to the clinic on July 1, 1926, complaining of increasing constipation, much gas, bloating and loss of weight.

Examination did not reveal gross abnormalities. The patient weighed 15 pounds (6.8 Kg.) less than she said she customarily weighed. The concentration of hemoglobin was estimated as 72 per cent; erythrocytes numbered 4,370,000 and leukocytes, 9,800. Roentgenologic examination of the colon after a barium enema

disclosed a filling defect of the cecum. Roentgenograms of the thorax gave negative results. In the absence of other suggestive signs and symptoms, the diagnosis could be carried no further than suspected lesion of the cecum. Exploration revealed adhesions between the cecum and lateral abdominal wall, but no tumor to cause the filling defect. There was also chronic cholecystitis with chronic cholelithiasis and a chronically inflamed appendix.

Cases 20, 21 and 22 belong in a group in which diagnosis and treatment are particularly difficult. An extensive resection such as that employed in case 20 would be unsuitable in many such cases because of surgical risk, and because it is most difficult to pick out just the right cases in which this procedure is helpful. In case 20 the patient has remained entirely free from symptoms for more than a year. Prolapse of the cecum into the pelvis has been frequently described. The fact that it sometimes causes a palpable tumefaction and even deformity, revealed by roentgenologic examination, indicates exploration as the best means of learning the method by which relief can be given. Furthermore, other conditions are found often enough to aggravate or account for the symptoms. Although undoubtedly there will be cases in which surgical measures will not be helpful, it seems best that operation be undertaken in most of them.

COMMENT

In any differential diagnosis of tumors of the ileocecal region, malignant disease must be given first consideration. Carcinoma is the most common of the malignant conditions; lymphosarcoma occurs rather rarely. Hyperplastic tuberculosis also has some significance. Actinomycosis is rare. The other benign tumors, such as cholesteatoma, lipoma, leiomyoma, mucous cyst and hemorrhagic infarction are rare and yet must be considered in the differential diagnosis.

It is gratifying to establish without exploration that the lesion is not malignant, but to be certain of this is difficult. Renal enlargement and retroperitoneal lesion should not be difficult to distinguish from ileocecal lesion. The roentgenogram has in a large measure done away with the former differential difficulty. The greater difficulty in diagnosis is that illustrated in the first ten cases of this series. In such cases there are a palpable mass and positive roentgenologic data, and yet the appearance of the patient is not that of the usual one presenting a malignant lesion in this situation. In these cases, the history offers the most important clue. The usual absence of anemia and the patient's general sense of well-being also offer important differential suggestions. Finally, the roentgenogram should be carefully studied to determine whether or not there is a filling defect typical of a malignant condition; this type of filling defect is rarely present in such cases.

OCCUPATIONAL THERAPY IN THE TREATMENT OF FRACTURE OF THE JOINT*

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Three and one-half years ago, Dr. Carl G. Burdick, director of the fourth surgical division, Bellevue Hospital, formulated certain principles for the care of patients with acute fracture. At that time it was decided to use occupational therapy in preference to massage and physiotherapy in the treatment of fracture of the joint. On the children's surgical service, Dr. Burdick had encountered six cases of myositis ossificans in fractures about the elbow. In all of these cases massage had been used, and this was considered the etiologic factor in producing the myositis. Therefore it was thought that vigorous massage might produce the same changes in adults, though to a lesser degree.

MYOSITIS OSSIFICANS

The following cases of myositis ossificans occurred in the children's surgical service:

CASE 1.—A child, aged 10, received a fracture of the internal condyle of the humerus on Aug. 9, 1920, and was referred for baking and massage to overcome the restriction in the motion of the elbow. Figure 1*A* shows the bony changes in the muscle around the elbow. This picture was taken four months after the injury. After baking and massage were discontinued, the condition improved. Figure 1 *B* shows most of the callus absorbed; the roentgenogram was taken seventeen months following the injury, or thirteen months following figure 1 *A*.

CASE 2.—A patient, aged 10, received a fracture of the internal condyle of the humerus on July 23, 1920, and was given baking and massage. The original plates, which showed the bony changes in the muscles, could not be found, but figure 2, which was taken one and one-half years following the accident, showed bony changes in the muscle.

The other cases in this series showed similar conditions and for that reason are not presented.

USE OF OCCUPATIONAL THERAPY IN FRACTURE

During the past three and one-half years 843 fractures have occurred in the fourth surgical division; of this number, 612 have been referred to the occupational therapy department. For the past six months, 68 cases have been referred for occupational therapy, including 19 cases

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Fig. 1.—*A*, roentgenogram taken four months after injury showing bony changes in muscle around elbow following baking and massage; *B*, roentgenogram taken seventeen months following injury showing most of the callus absorbed.

Fig. 2.—Roentgenogram taken one and one-half years following accident still showing some bony changes in muscle around elbow.

Fig. 3.—*A*, comminuted fracture of the lower end of the radius before reduction; *B*, same fracture after reduction.

of Colles' fracture, 12 of Pott's fracture, 5 of fracture of the upper third of the tibia, 5 of fracture of the surgical neck of the humerus, 4 of fracture of the upper third of the fibula, 4 of fracture of the condyles of the humerus, 4 of fracture of the patella, 3 of fracture of the lower third of the radius, 2 of fracture of the greater tuberosity of the humerus, 2 of fracture of the clavicle, 2 of epiphyseal separation of the wrist, 2 of fracture of the lumbar spine, 1 of fracture of the upper third of the femur, 1 of fracture of the lower third of the femur, 1 of fracture of the lower third of the radius and ulna and 1 of dislocation of the elbow.

Fig. 4.—*A,* a patient doing block printing to increase flexion and extension of the wrist; *B,* the patient using a hammer to increase the grasping power of the hand.

Miss Mary E. Merritt, director of the occupational therapy department at Bellevue Hospital, is responsible for the outline of treatment for the individual cases, and for the general supervision of the work. Casts are removed and occupational therapy is started early in all types of cases: as a general rule, in ten days for Colles' fracture or for fractures about the wrist, and in two or three weeks for Pott's fracture or for fractures about the ankle. The treatment for other types of fractures depends on the individual case. These patients report for treatment three times a week; during each visit they receive three work periods, alternating with rest periods. The work periods vary from three to ten minutes, or until the patients become fatigued. They are

Fig. 5.—*A*, exercise done at home to increase the motion of the fingers; *B*, exercise done at home to flex and extend the wrist.

Fig. 6.—A patient who could not be interested in block printing is obtaining flexion and extension with an elastic band.

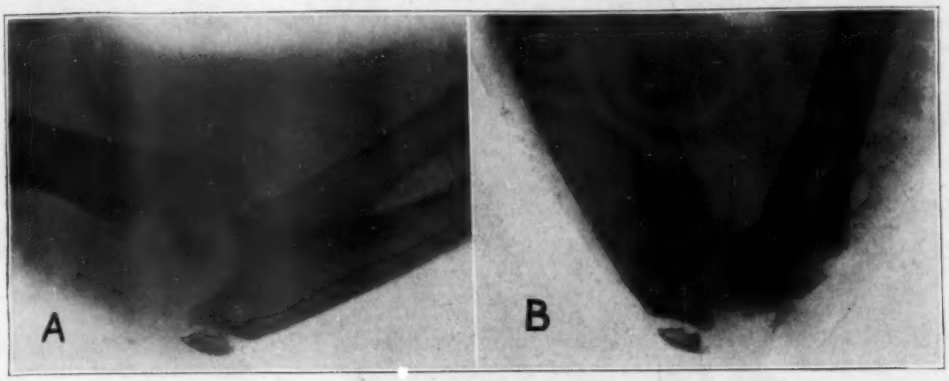

Fig. 7.—*A*, fracture dislocation of the elbow; *B*, the same fracture, after reduction.

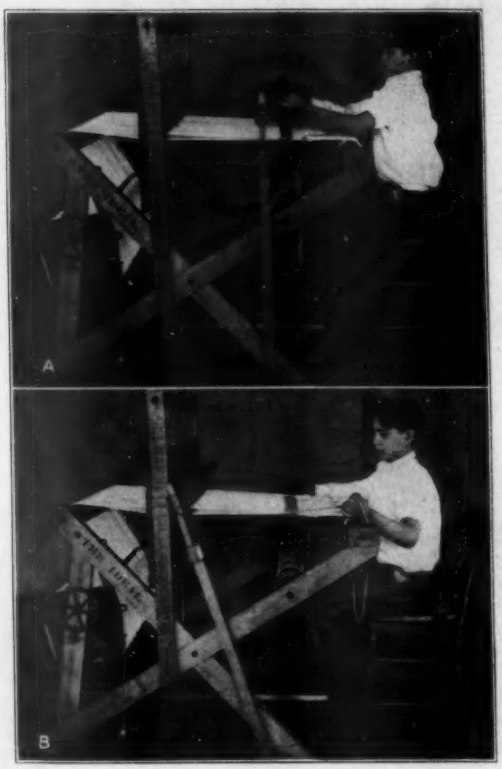

Fig. 8.—*A*, extension and pronation of the forearm; *B*, flexion and supination of the forearm.

then given a rest period of five minutes, followed by a second work period. This again is followed by a rest period of five minutes, and finally a third work period. The work periods are gradually increased and the rest periods diminished as the patients progress during the course of treatment.

Fractures About the Wrist.—Fractures about the wrist constitute the highest percentage of the cases seen. Figure 3*A* shows a comminuted fracture of the lower end of the radius before reduction; figure 3*B* was taken after reduction. This represents a difficult case. To get a good functional result in this type of fracture, motion should be started within fourteen days. When first referred for treatment, the patient is given block printing to do, as illustrated in figure 4*A*

Fig. 9.—Flexion and extension of the forearm.

and *B*. This improves the grasping power of the hand, and increases flexion and extension of the wrist. A tack hammer is used at the beginning and the weight of the hammer is increased until the patient can use a 10 ounce hammer. In addition, the patients are given exercises to do at home, as illustrated in figure 5*A* and *B*. In figure 5*A* the patient holds the fingers and thumb extended and touches each finger to the thumb ten times, night and morning. This number is increased until the exercise is done twenty times. Figure 5*B* shows the hands clasped together; the wrist is flexed and extended ten times, night and morning, and this is gradually increased to twenty times. Some patients cannot be interested in block printing. Figure 6 demonstrates a patient using an elastic band to obtain flexion and extension of the wrist.

Fractures About the Elbow.—In these cases early motion is essential, and damage can be done by vigorous massage, as was illustrated in

the cases of myositis ossificans. Figure 7*A* shows a fracture dislocation of the elbow, and figure 7*B* the same fracture after reduction. When treatment is started, flexion and extension of the elbow, and pronation and supination of the forearm must be obtained. Figure 8*A* shows the

Fig. 10.—*A*, different method of obtaining flexion of the forearm; *B*, extension of the forearm.

Fig. 11.—Exercise done at home in cases of fracture of the elbow.

patient obtaining extension of the elbow and pronation of the forearm; in figure 8*B* he is obtaining flexion of the elbow and supination of the forearm, while in figure 9 the patient is obtaining flexion and extension. For patients who cannot be interested in this type of work, figure 10*A* illustrates how flexion of forearm is achieved by a different method.

Fig. 12.—Fracture of the surgical neck of the humerus.

Fig. 13.—Abduction and extension of the arm above the head during treatment.

Fig. 14.—*A*, anteroposterior view of a fracture of the lower end of the fibula; *B*, lateral view of the same fracture.

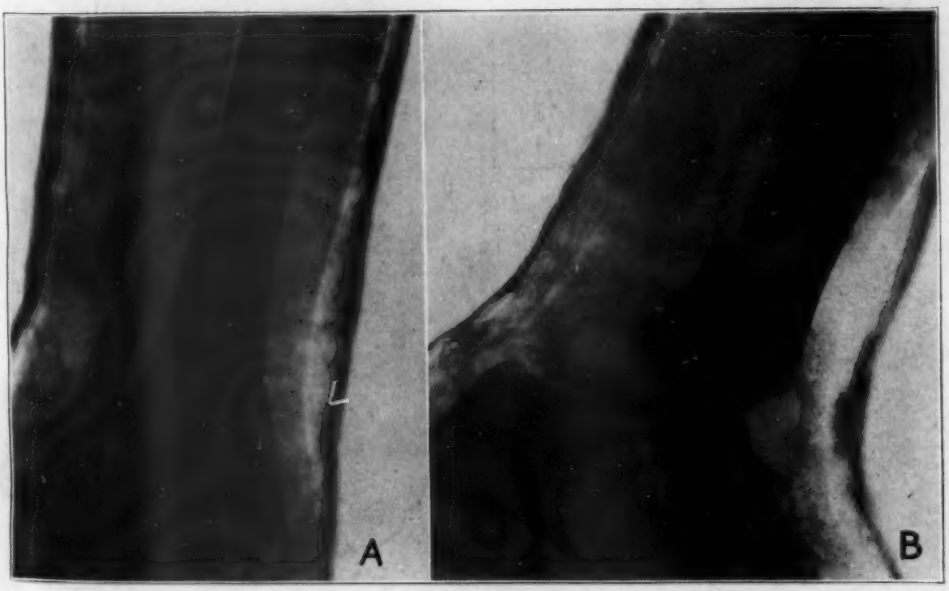

Fig. 15.—*A*, anteroposterior view of the fracture shown in figure 14, after reduction; *B*, lateral view after reduction.

Figure 10*B* illustrates extension of the forearm, while figure 11 illustrates the exercise which is done ten times night and morning at home in cases of fracture of the elbow; it is gradually increased to twenty times.

Fractures About the Shoulder.—This type of fracture is frequently seen in elderly people. Figure 12 shows a fracture of the surgical neck of the humerus. It is important to obtain abduction of the arm from the body and extension above the head. Figure 13 shows the patient accomplishing both during treatment.

Figure 16

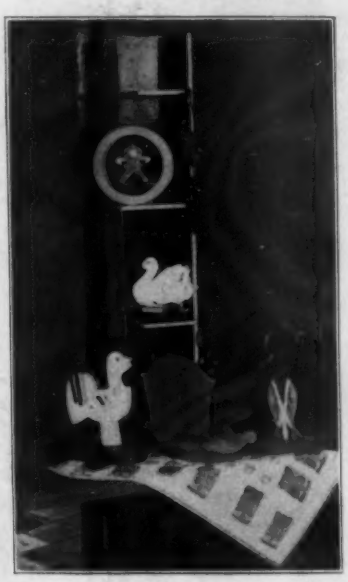

Figure 17

Fig. 16.—A patient using the treadle saw to improve the motion of the ankle.

Fig. 17.—Articles completed by a patient during a six weeks' period of treatment.

Fractures About the Ankle.—Next to injuries of the wrist fractures about the ankle are seen most frequently. Figure 14*A* is an anteroposterior view of a fracture of the lower end of the tibia and fibula. Figure 14*B* is a lateral view of the same fracture, while figure 15*A* is an anteroposterior view after reduction, and figure 15*B* a lateral view after reduction. It is important to obtain early motion in this type of case. Figure 16 demonstrates a patient sawing wood on a treadle saw, the foot piece of which is similar to that of a sewing machine. First, the patient is given soft white wood one fourth of an inch thick; he makes a small object, such as a shade pull. The thickness of the wood

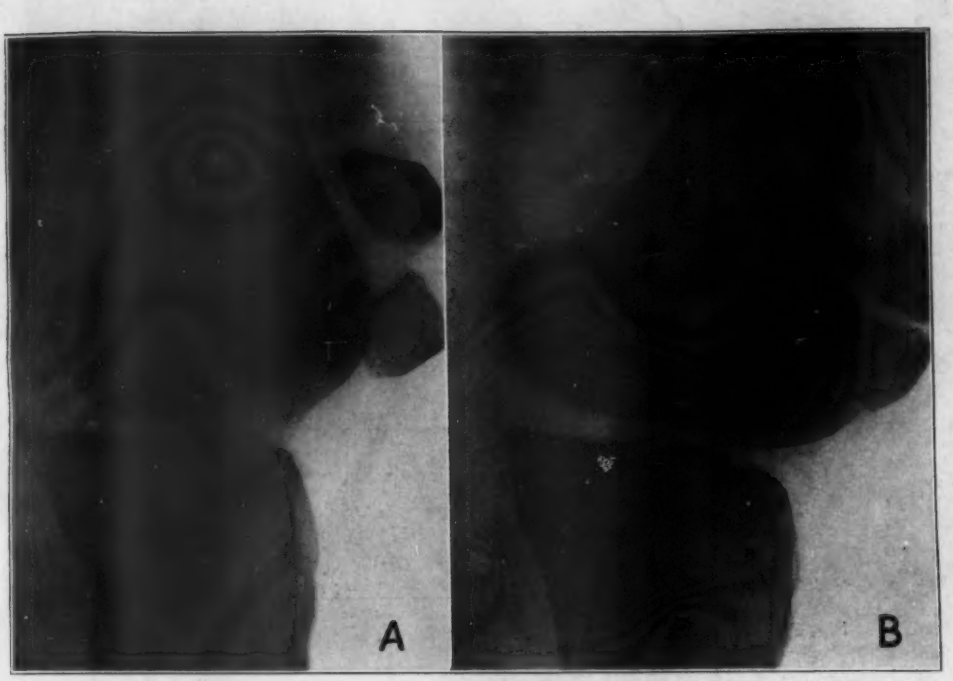

Fig. 18.—*A*, fracture of the patella; *B*, the same fracture after operation.

Fig. 19.—Fracture of the external tuberosity of the tibia extending into the joint.

Fig. 20.—A patient using a machine for flexion and extension of the knee.

Fig. 21.—A patient who could not be interested in machine work, using an elastic band.

is gradually increased as the patient's condition improves; the size of the object sawed is also increased. During the rest period, the patient sandpapers the wood, puts the article together, and finally paints it. Figure 17 represents the articles made by a patient with a fracture about the ankle, during a six weeks' period of treatment. These articles were entirely completed by the patient. The ones at the top of the picture are small and are made of thin wood, while those at the bottom are larger and of heavier wood.

Fig. 22.—Central fracture of the acetabulum.

Fractures About the Knee.—It is important for patients with this injury to be able to obtain 90 degrees of flexion. Figure 18*A* shows a fracture of the patella. Figure 18*B* shows the same fracture after an open operation had been performed, and the ligamentum patellae and capsule had been sutured with fascia lata. Figure 19 shows a fracture involving the external tuberosity of the tibia, and extending into the knee joint. Figure 20 shows the patient working on a machine with a yardstick attached for the purpose of measuring the increase in flexion and extension. Figure 21 shows a patient who could not be interested in any machine work and who obtained flexion by means of an elastic.

Fig. 23.—The fracture shown in figure 22, after a Steinman pin had been inserted through the greater trochanter; the roentgenogram was taken twelve hours after the insertion of the pin.

Fig. 24.—*A*, flexion of the knee and hip; *B*, extension of the leg.

Fractures About the Hip.—Fractures about the hip are represented by fractures of the neck of the femur and by fractures involving the acetabulum of the pelvis. Figure 22 shows a central fracture of the acetabulum. Figure 23 shows the same fracture after reduction has been accomplished by means of a Steinman pin inserted through the greater trochanter. Figure 24*A* shows the patient obtaining flexion of the knee and hip, while figure 24*B* shows extension of the leg. Figure 25 illustrates the method of obtaining abduction of the thigh. In all types of fracture, exercise was prescribed for night and morning at home.

Fig. 25.—Abduction of the leg.

Miss Meritt had occasion to observe patients with fractures, referred from other surgical divisions in the hospital, on whom occupational therapy and massage were employed, but these patients did not progress so satisfactorily as those on whom occupational therapy alone was used. It is essential to have trained instructors to supervise the work. One instructor can treat twenty patients in half a day.

All patients with fractures of the joint in the fourth surgical division are referred for treatment to the occupational therapy department, in preference to the department for physiotherapy.

125 East Seventy-Second Street.

CORRELATIONS OF INTERNAL AND EXTERNAL PANCREATIC SECRETION

IV. EFFECT OF ISOLATION OF TAIL OF PANCREAS ON CARBOHYDRATE METABOLISM *

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In previous communications, one of us (G. de T.[1]) reported studies of the histology of the tail of the pancreas after it had been excluded from the rest of the gland and its external secretion had stopped. The splenic portion of the pancreas was isolated in twenty-five dogs, and specimens were taken from two days to one year at intervals. After a short period of edema, a gradual increase in connective tissue occurred, first around and then within the lobules, resulting in a pancreatic cirrhosis. The ducts were first dilated, then showed proliferation and infolding of their epithelium. A number of minute ducts appeared. The islands showed edema for the first two weeks; later large solid cell complexes appeared showing the vascular arrangement and staining properties of islet tissue. Such an isolated tail did not tend to degenerate and undergo absorption for at least three months if a free transplant was made into the omentum.

Furthermore, one of us and Nathanson,[2] in studying the diastase content in the blood following ligation of the tail, found that the high diastase values returned to normal in two weeks. In later experiments, it was found that even after artificial stimulation the diastase would not rise above the normal limits after three weeks.[3]

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* From the Departments of Surgery and Physiology, Northwestern University Medical School, with the aid of an Elizabeth J. Ward Fellowship in Surgery.

1. De Takats, G.: Correlations of Internal and External Pancreatic Secretion: I. General Considerations and Review of the Literature, Arch. Surg. **19**:771 (Nov.) 1929; II. The Histologic Changes in the Isolated Tail of the Pancreas, ibid. **19**:775 (Nov.) 1929.

2. De Takats, G., and Nathanson, I. T.: Correlations of Internal and External Pancreatic Secretion: III. The Effect of Ligation of the Tail of the Pancreas on Diastase in the Blood, Arch. Surg. **19**:788 (Nov.) 1929.

3. De Takats, G., and Nathanson, I. T.: Unpublished data.

Thus we have evidence of a persistence and even a hyperplasia of the islet tissue, with histologic and chemical evidence that the external secretion has subsided from the isolated tail of the pancreas. The tail of the gland, wrapped up in omentum to ensure better vascularization and possibly counteract a progressing sclerosis, has been turned into a ductless gland.

The purpose in this paper was to try to demonstrate the function of this separated tail. The hypertrophy and numerical increase of islets, if they are functioning, might manifest themselves in an increased insulin output from the gland. Selection of a suitable method for demonstrating an increase in insulin seemed desirable.

SELECTION OF METHOD

Direct evidence of an increased output of insulin would be the determination of insulin in the blood and tissues of experimental animals before and after such operations. However, this laboratory has not been successful up to the present time in determining insulin in the blood of normal animal or man either with the Doisy-Somogyi and Shafer or with the Dickens and Dodds or the Moloney-Findlay method.[4] Another possibility, namely, the demonstration of increased dextrose-fixation of the red cell, as suggested by Loewi and Häusler,[5] was considered but abandoned as the reaction did not seem specific and could not be reliably reproduced later by the originator of the method.[6]

We had to content ourselves then with a search for indirect evidence, namely, through the action of insulin on carbohydrate metabolism. Mansfeld,[7] who was first to suggest an increase in sugar tolerance following ligation of the tail, used an oral sugar tolerance test to demonstrate a better utilization of carbohydrates. He emphasized the appearance of a starvation hypoglycemia after forty-eight hours of fasting, which was not present in the normal animal. He also reported a lowering of the blood sugar during fasting following ligation of the tail.

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4. Ivy, A. C.: Personal communication to the authors.

5. Loewi, O., and Häusler, H.: Ueber hormonale Vorgänge nach Glukosezufuhr, Arch f. exper. Path. u. Pharmakol. **123**:88, 1927.

6. Loewi, O.: Insulin und Glykemin, Klin. Wchnschr. **8**:391 (Feb. 26) 1929.

7. Mansfeld, G.: Versuche zu einer chirurgischen Behandlung des Diabetes, Klin. Wchnschr. **3**:2378, 1924; Versuche zu einer operativen Behandlung des Diabetes, ibid. **6**:105, 1927. Mansfeld, G., and Szirtes, L.: Ueber die Beziehungen zwischen äusserer und innerer Secretion der Drüsen, Arch. f. exper. Path. u. Pharmakol. **130**:1, 1928. Mansfeld, G., and Schmidt, F.: Versuche zu einer chirurgischen Behandlung des Diabetes, Klin. Wchnschr. **7**:1457 (July 29) 1928.

Alpern and Leites,[8] Nather, Priesel and Wagner,[9] Jorns[10] and Alpern and Besuglow[11] confirmed the observation of increased sugar tolerance following ligation of the tail. Nather, Priesel and Wagner, in their second article,[12] Wohlgemuth and Seo,[13] Galehr and Ladurner and Unterrichter[14] could not confirm Mansfeld's results.

Jorns,[15] in a most comprehensive work on this subject, analyzed the differences in the animals used for experimentation and the discrepancies of surgical technic that may have influenced the results.

Alpern and Besuglow[11] noted changes in fat tolerance after the ligation of the tail, and noted an increase in the weight of the dogs operated on. Furthermore, a change in the potassium-calcium ratio and an increase in alkali reserve were noted. This would indicate a diminution in sympathetic tonus exactly the opposite of what Wohlgemuth[13] found.

Realizing that none of these methods would offer a direct proof of increased insulin output, and that none of them would consider the compensatory attempts of the normal animal, even if such increased secretion were present, we selected methods that would give at least indirect evidence that a change in carbohydrate utilization had taken place.

FACTORS THAT INFLUENCE SUGAR TOLERANCE

A sugar tolerance curve is the result of several factors, which must be considered briefly.

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8. Alpern, D., and Leites, S.: Ueber den Einfluss der Unterbindung des Ductus pancreaticus auf den Blutzucker, Klin. Wchnschr. **4**:1551, 1925.

9. Nather, K.; Priesel, R., and Wagner, R.: Die Beeinflussung des Blutzuckerspiegels durch Unterbindung der Ausführungsgaenge der Bauchspeicheldrüse beim Hund, Klin. Wchnschr. **5**:932, 1926.

10. Jorns, G.: Ueber des Verhalten der endokrinen Pankreasfunktion nach Unterbindung der Ausführungsgaenge, Klin. Wchnschr. **5**:2434, 1926; Die Sklerose des Pankreas nach Unterbindung des Ausführungsgaenges und die Transplantation des sklerotischen Gewebes, Beitr. z. klin. Chir. **139**:325, 1927.

11. Alpern, D. E., and Besuglow, W. P.: Beobachtungen ueber die Hyperfunktion des Inselapparates der Bauchspeicheldrüse, Klin. Wchnschr. **7**:586 (March 25) 1928.

12. Nather, K.; Priesel, R., and Wagner, R.: Die Beeinflussung des Blutzuckerspiegels durch Unterbindung der Ausführungsgaenge der Bauchspeicheldrüse beim Hund, Klin. Wchnschr. **6**:2089, 1927.

13. Wohlgemuth, Julius; and Seo, T.: Ueber experimentälle Erzeugung von chronischer Sympathicotonie beim Kaninchen, Ztschr. **164**:271, 1925.

14. Galehr, O.; Ladurner, P., and Unterrichter, L.: Des Verhalten der Blutzuckerwerte nach Pankreasunterbindung, Pflüger's Arch. f. d. ges. Physiol. **218**: 477, 1928.

15. Jorns, G.: Experimentelle und klinische Beiträge zur Pathologie der Langerhansschen Inseln des Pankreas, Beitr. z. klin. Chir. **146**:1, 1929.

Site of Administration.—The subcutaneous route was painful when hypertonic concentrations were used. If concentrations of 5 and 10 per cent were used, the pressure of the great fluid volume made the animal restless and possibly excited. Thus another undesirable factor was introduced. The intraperitoneal administration of from 2.5 to 3 Gm. of dextrose per kilogram of body weight was given serious trial. The absorption of dextrose is uniform and rapid. It may be influenced, however, by operative procedures which damage the intact peritoneal surface. It also dehydrates the animal and thus may influence the blood sugar readings. Two of us (G. de T. and I. J. Seitz [16]) used this form of administration for more than a year. It was finally discontinued. Oral administration seems desirable, being the most physiologic entry of the dextrose into the body. The necessity of using the same concentration of dextrose for comparative curves is important. In the greater part of our experiments, we used small repeated doses of sugar, the exact technic of which will be described later. Finally, the intravenous administration of dextrose, with the help of a Woodyatt pump, was also used in our later experiments. As Woodyatt, Sansum and Wilder [17] pointed out, tolerance is more of a question of velocity, not so much of weight. The pump enabled us to administer accurate quantities of dextrose per hour. It also eliminated the variations of absorption from the site of administration.

The Amount of Dextrose Ingested.—It was felt that for our work undertaken to demonstrate a possible increase of insulin output of the gland, smaller amounts should be used than is customary in sugar tolerance tests. Smaller amounts of dextrose cause a smaller increase in blood sugar, and a change in the insulin output might be more easily detected. It was furthermore felt that a repeated dose of dextrose, as suggested by Traugott,[18] Staub [19] and Lennox,[20] would demonstrate the presence or increase of adequate insulin response much better than a single dose. Thus the amount of available insulin would be apparent not only by the height of the curve, by the rapidity of returning to the

16. De Takats, Geza; and Seitz, Ira J.: Unpublished data.

17. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **45**:2067 (Dec. 11) 1915.

18. Traugott, K.: Ueber das Verhalten des Blutzuckerspiegels bei wiederholter und verschiedener Art enteraler Zuckerzufuhr und dessen Bedeutung für die Leberfunktion, Klin. Wchnschr. **1**:892, 1922.

19. Staub, H.: Ueber das Verhalten des Blutzuckers nach Verabfolgung kleiner Glucosemengen, Ztschr. f. klin. Med. **91**:44, 1921.

20. Lennox, W.: Stimulation of the Sugar Regulating Mechanism as Shown by Duplicate Blood Sugar Curves, J. Biol. Chem. **73**:237 (March) 1927.

normal level and by the posthyperglycemic hypoglycemia, but also by the flattening out of the second curve, as can also be observed in normal subjects.

Noorden found that in light cases of diabetes, the first curve may show a normal return and that only the second curve reveals a typical diabetic abnormality. We have regularly been able to see the flattening out of the second curve in normal dogs, and feel that such a double sugar curve may give more information as to the response of the pancreas to hyperglycemia. So far as we could gather from the literature, Hamman and Hirschmann [21] were the first to use duplicate curves in man, long before the insulin era.

Time of Fasting and Character of Previous Diet.—It has been repeatedly stated since Bang's initial observation,[22] that previous undernourishment or starvation will provoke an alimentary hyperglycemia; conversely, a curve taken a few hours after a meal is usually abnormally flat. In comparing curves, then, it must be postulated that the tolerance tests are run after the same period of fasting. According to Staub,[19] patients fed on a diet containing protein and fat showed definitely higher curves than patients on a diet containing carbohydrate. Experimental animals then must be kept on an identical diet during the entire experiment.

Effect of Fear and Struggling.—One of the most important sources of error may be to compare subsequent tolerance curves in the animal and not consider the emotional effect of the stomach tube on the sugar curve. We show a fairly typical chart of three preoperative curves in the dog under identical conditions. We are convinced that the first alimentary hyperglycemia test is invariably too high, and that dogs should be trained to be in a relaxed, basal condition before tests of sugar tolerance are undertaken. The effect of the sympathetic nervous system on blood sugar is too well known to omit such a precaution. It can be readily seen that if in the case of dog 2 (chart 1) any therapeutic procedure had been carried out after the first curve, it would have led to the assumption that a great increase in tolerance took place. The gentle handling of the unfrightened animal is equally important in the intravenous sugar tolerance tests. We have rejected several of these as the initial blood sugar was found to be too high. Cannon's students, who showed glycosuria after examination,[23] offer a striking example of emotional glycosuria.

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21. Hamman, Louis; and Hirschmann, J. J.: Effects upon the Blood Sugar of Repeated Ingestion of Dextrose, Bull. Johns Hopkins Hosp. **30**:306, 1919.

22. Bang, J.: Der Blutzucker, Wiesbaden, 1913.

23. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton & Company, 1918, p. 75.

It seemed necessary to discuss these elements of error before stating our own method, because many previous workers who have claimed increased or decreased sugar tolerance after ligation of the pancreatic tail have not mentioned precautions to eliminate these factors, nor have they run series of determinations over a long enough period to justify conclusions.

METHODS OF EXPERIMENTATION

Healthy dogs, weighing from 10 to 15 Kg., were used. They were accustomed to kennel life and were fed a well balanced standard diet once a day. Food was omitted for eighteen hours before any experiment was made. A sample of venous blood was taken, after which 10 Gm. of dextrose in 20 per cent solution was given by stomach tube. One hour later another identical dose of dextrose was given. Samples of blood were taken every fifteen minutes after each dose of dextrose for one hour, so that altogether nine samples of blood were analyzed for sugar with the Folin-Wu method. At least two satisfactory curves were obtained before the operation. In some dogs, from three to four preoperative determina-

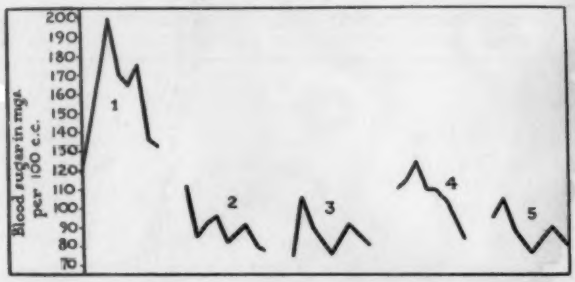

Chart 1.—Effect of emotion, feeding and starvation on oral sugar tolerance curves. Two grams of dextrose in 20 per cent solution was given by stomach tube twice, at one hour intervals. 1 stands for the emotional curve (dog struggled and was frightened); 2, dog was fed two hours previous to test; 3, dog was fed forty-two hours previous to test; 4 and 5, dogs were fed eighteen hours previously. The two latter are regarded as correct preoperative curves.

tions were made before a satisfactory curve could be obtained. The isolation of the tail of the pancreas was then undertaken, as described in a previous communication.[24] In this series, the electric cautery was used and the tail was wrapped up in omentum. We lost one dog under anesthesia, but none following the operation.

After the animal recovered satisfactorily, tolerance curves were determined once a month. In some dogs curves were obtained at closer intervals. In this series we have five dogs operated on for six months or longer. From a previous series, ten dogs were carried over eighteen months, but as they were chiefly used for histologic studies, we felt that the repeated pancreatic excisions and omental transplants would interfere with the sugar tolerance curves. They were not used. In two dogs of this series epinephrine hyperglycemia curves have been determined

24. De Takats (footnote 1, second reference).

before and after the operation. After a sample of venous blood has been taken, 10 cc. of a 1:10,000 solution of epinephrine has been injected intravenously. Samples of blood were taken at half hour intervals up to two hours.

Furthermore, in the same five dogs intravenous sugar tolerance tests have been performed with the Woodyatt pump. Unfortunately, determinations were not made before the operation, so that as a basis of normal tolerance the numerous determinations made by Woodyatt, Sansum and Wilder,[17] Felsher and Woodyatt[25] and Jordan[26] were utilized. From Woodyatt's original work it would seem that 0.9 Gm. of dextrose per kilogram of body weight per hour is the maximal amount of sugar that can be injected without producing glycosuria. From the work of Woodyatt and Felsher elaborated by Jordan, it seems that by prolonging the intravenous administration of dextrose to several hours, more and more dextrose could be utilized. We have simply used 1, 1.5 and 2 Gm. of dextrose per hour per kilogram of body weight to determine whether an increase of tolerance to this type of dextrose administration has taken place. Dextrose was injected in 5 and 10 per cent solutions, and urine was collected before and after the injection at a timed rate. The sugar, if present, was determined quantitatively by the Benedict method. Occasionally, blood sugar determinations were

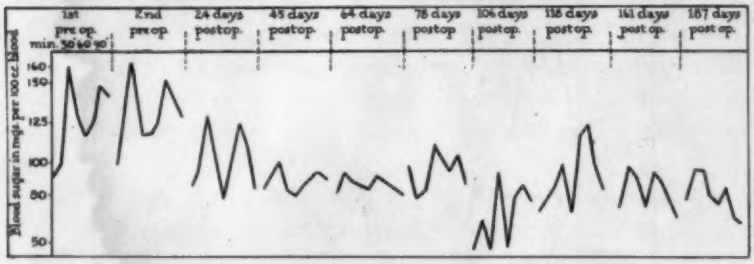

Chart 2.—Double sugar tolerance curves obtained on dog 1, a white male, weighing 21 pounds (9.5 Kg.). Two doses of 10 Gm. of dextrose in 20 per cent solution were given by stomach tube at one hour intervals. The dog maintained his weight and was in good condition throughout the entire experiment.

made during the experiment. Finally, dogs were starved for two days after the blood sugar during fasting was taken, and a sample of blood was analyzed every morning. According to Mansfeld, this "Karenzhypoglycemie" was typical of the dogs operated on by his method.

RESULTS

Double Sugar Tolerance Curves.—Chart 2 illustrates the results obtained in dog 1. Following two correct preoperative curves, the postoperative curves show a marked fall in the blood sugar values during fasting together with a depression of the maximum rise following the

25. Felsher, Hannah, V., and Woodyatt, R. T.: Studies on the Theory of Diabetes: Sugar Injection Curves in Dogs Under Intravenous Injection of Glucose At Lower Rates, J. Biol. Chem. **60**:737, 1924.

26. Jordan, E. M.: Effect of Injected Glucose on Tolerance, Am. J. Physiol. **80**:441 (April) 1927.

ingestion of sugar. The lowest blood sugar during fasting was obtained one hundred and six days following operation, namely, 48.7 mg. per hundred cubic centimeters of blood. The average maximal rise in blood sugar was 73 per cent before the operation; the smallest postoperative rise was obtained on the sixty-fourth day, namely, 18.75 per cent. On the seventy-eighth day, the ingestion of 10 Gm. of dextrose resulted in an initial hypoglycemia, followed by a rise in blood sugar. From here on the curves become steeper and less regular on the one hundred and sixth and one hundred and eighteenth days, while the last two curves show a normal appearance. Even the last two curves, as all others, show a lower initial and maximal value in blood sugar than the preoperative curves. The maximal rise in blood sugar is 24.5 and 21.5 per cent in the last two curves. Also the posthyperglycemic hypoglycemia is marked, as values of 66.6 and 57.1 mg. per hundred cubic

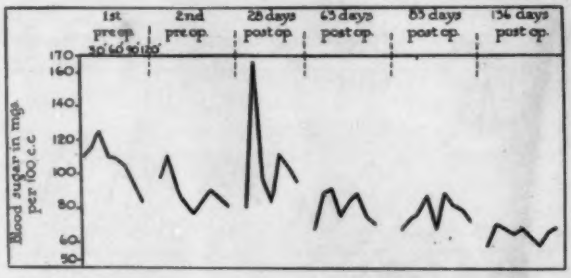

Chart 3.—Double sugar tolerance curves obtained on dog 2, a brindle male, weighing 22 pounds (10 Kg.). Ten grams of dextrose in 20 per cent solution was given at one hour intervals. Note the marked hypoglycemia following the double dose of dextrose before the operation. The high value in the first postoperative curve is open to question.

centimeters of blood were obtained on the one hundred and sixty-first and one hundred and eighty-seventh postoperative day. Throughout the whole period the dog maintained his initial weight of 21 pounds (9 Kg.).

Chart 3 illustrates the results obtained in dog 2. Following two preoperative curves which indicate a marked fall in blood sugar after a double dose of dextrose, four postoperative curves are available. The curve on the twenty-eighth day shows a sudden rise to 166.6 mg. per hundred cubic centimeters of blood, which reading may be questioned. Subsequent curves show a gradual decline in the values during fasting and the peaks. The lowest value during fasting of 59.3 mg. per hundred cubic centimeters was obtained on the one hundred and thirty-sixth day. The average percental rise in blood sugar was 15.5 before the opera-

tion; the smallest rise after the operation was from 59.3 to 71.5 mg., a rise of 20.6 per cent. The dog weighed the same during the entire experiment, except for a temporary loss of 3 pounds (1.4 Kg.) following the operation.

Chart 4 illustrates the results obtained in dog 3, a black and white male, weighing 25 pounds (11.3 Kg.). The first preoperative curve was taken after forty-two hours of fasting, thus explaining the unusual rise following the administration of 10 Gm. of dextrose. The second curve is quite flat. The lowest value during fasting was reached on the thirty-fifth postoperative day, namely, 51.2 mg. per hundred cubic centimeters of blood. Subsequent curves do not show marked changes from the initial tolerance, although there is an instability of the sugar regulating mechanism on the one hundred and twenty-fourth day. The dog was in good shape and maintained his weight through the entire experiment.

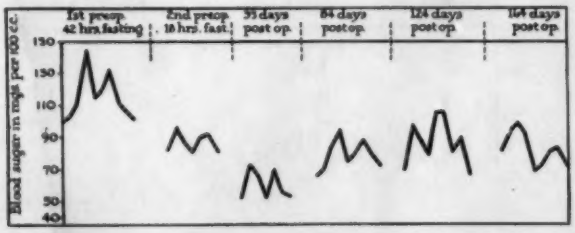

Chart 4.—Double sugar tolerance curves of dog 3, a black and white male, weighing 25 pounds (11.3 Kg.). Note the differences between the first and second preoperative curves, owing to different fasting periods before the feeding of dextrose. Ten grams of 20 per cent dextrose solution was given by stomach tube at one hour intervals. The dog looked sick and had running nose and eyes on the hundred and twenty-fourth day.

Chart 5 illustrates double sugar tolerance curves obtained on dog 4, a white male, weighing 30 pounds (13.6 Kg.). One-half gram of dextrose per pound of body weight was given in 20 per cent solution at zero and one hour. A remarkable curve was obtained on the twenty-seventh day, when the sugar level of 80 mg. per hundred cubic centimeters of blood fell to 57.1 mg. as a posthyperglycemic reaction. The curve on the ninety-seventh day shows a definite diminution of tolerance and shows a characteristic diabetic curve. The dog was in good condition and showed no glycosuria. There was a loss in weight in the first few weeks, but the dog regained his weight on the usual diet.

Chart 6 illustrates double sugar tolerance curves for dog 5, a male black bull dog weighing 26 pounds (11.8 Kg.). One gram of dextrose

per pound of body weight was given in two doses at an hour's interval. The lowest level during fasting and the lowest peak was obtained on the thirtieth day. On the seventy-ninth day, the curve still did not reach the preoperative level, and the secondary rise was delayed as compared to the preoperative curves. The dog was in good condition and did not lose weight during the experiment.

Epinephrine Curves.—Ten cubic centimeters of a 1 : 10,000 solution of epinephrine was slowly injected intravenously before and twice after

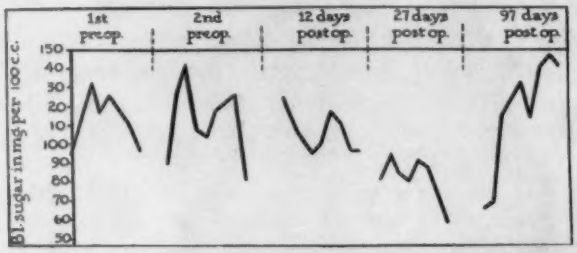

Chart 5.—Double sugar tolerance curves obtained on dog 4, a white male, weighing 30 pounds (13.6 Kg.). One gram of dextrose per pound of body weight was administered in 20 per cent solution in two doses at one hour intervals. Note the marked increase and decrease in tolerance on the twenty-seventh and ninety-seventh days.

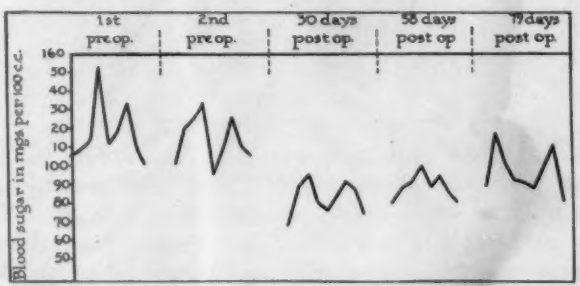

Chart 6.—Double sugar tolerance curves obtained on dog 5, a black male bull dog, weighing 26 pounds (11.8 Kg.). One gram of dextrose per pound of body weight was given in 20 per cent solution in two doses at one hour intervals. Note the gradual return to the original level, although the last curve on the seventy-ninth day does not reach the original level.

the operation into two dogs. The curve of dog 2 showed a slight rise followed by a marked fall one and one-half hours after injection. Twenty-eight days after the operation a peculiar inversion of the curve occurred, with a hypoglycemic value of 52.6 mg. per hundred cubic centimeters of blood, one hour after the injection followed by a sharp rise to 117.9 mg. One hundred and thirty-five days after the operation

the epinephrine curve was similar to the first one, with the exception of slightly lower values. Dog 3 showed a sharper rise in blood sugar than dog 2, and the curve did not drop under the initial level. Forty-seven days after the operation, a marked imbalance in carbohydrate regulation was brought about by the injection of epinephrine. The blood sugar fell and rose twice within two hours following the injection. During the same period, the dextrose tolerance curves of this dog showed low values during fasting and slight rises. One hundred and sixty-three days after the operation, the epinephrine curve showed the usual form, except for a higher level, than the preoperative curve. One cannot be sure that this dog had not fasted too long before the first epinephrine curve was made, which would explain the low level of blood sugar during fasting, 57.1 mg. per hundred cubic centimeters (chart 7).

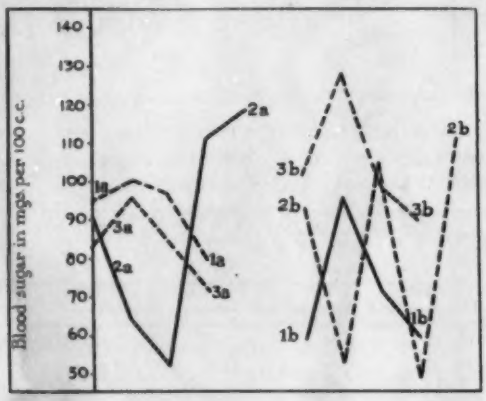

Chart 7.—Epinephrine hyperglycemia on dogs 2 and 3, before and twice after the operation. Ten cubic centimeters of 1:10,000 solution of epinephrine was injected into the dogs, after eighteen hours of fasting. Samples of blood were taken before, one half, one and two hours after injection. 1 *a* indicates the curve taken before operation; 2 *a*, twenty-eight days after operation; 3 *a*, one hundred and thirty-five days after operation; 1 *b*, before operation; 2 *b*, forty-seven days after operation; 3 *b*, one hundred and sixty-three days after operation. Note the inversion of curves in both dogs, which return to normal in the second postoperative curve.

Intravenous Sugar Tolerance Curves with Timed Rates.—The Woodyatt pump was used. One, 1.5 and 2 Gm. of dextrose in 5 per cent solution were injected per kilogram of body weight for one hour. The urine was tested for sugar before the experiment and in the first twenty-four hour specimen following the injection. A few blood sugar determinations were also made.

The tolerance of dogs following this type of administration was as follows:

TABLE 1.—*Intravenous Sugar Tolerance Curves on Dogs, with Separation of the Tail of the Pancreas. Five per Cent Dextrose Solution was Given at a Timed Rate* *

Dog	Postoperative Day	Dose per Kilogram per Hour, Gm.	Glycosuria, per Cent
1	193	2	...
2	145	1.5	...
2	145	2	0.3
3	130	1.5	...
3	130	2	0.7
4	115	1	1.2
5	165	1.5	...
5	165	2	1.1

* The upper limit of tolerance in the normal dog was 0.9 Gm. of dextrose per kilogram per hour (Woodyatt, Sansum and Wilder).

Dog 1, on the hundred and ninety-third postoperative day, received 2 Gm. of dextrose per kilogram per hour which did not cause glycosuria.

Dog. 2, on the hundred and forty-fifth postoperative day, received 1.5 Gm. of dextrose which caused no glycosuria; 2 Gm. of dextrose produced 0.3 per cent of sugar in the twenty-four hour specimen.

Dog 3, on the one hundred and thirtieth postoperative day, showed no glycosuria with 1 and 1.5 Gm. of dextrose per kilogram per hour. Two grams of dextrose produced a glycosuria of 0.7 per cent.

Dog 4, on the hundred and fifteenth postoperative day, showed a glycosuria of 1.2 per cent following the intravenous injection of 1 Gm. of dextrose per kilogram per hour.

Dog 5, on the hundred and sixty-fifth postoperative day, showed no glycosuria with 1 and 1.5 Gm. of dextrose. Two grams produced a glycosuria of 1.1 per cent.

No preoperative determinations with this type of tolerance were made. The highest amount of dextrose that would not cause glycosuria in the normal dog was taken as 1 Gm. per kilogram of body weight per hour, which is above the values given following numerous determinations of Woodyatt, Sansum and Wilder,[17] Woodyatt and Felsher [25] and Jordan.[26]

Blood Sugar Determinations on Fasting Dogs.—After eighteen hours of fasting, a blood sugar determination was made, followed by two more determinations twenty-four and forty-eight hours later, during which time the dogs did not receive anything but water. Table 2 illustrates our observations. The blood sugar level does not remain constant even in the normal dog, but may drop and rise within a limit of 20 mg. per hundred cubic centimeters of blood. Numerous and careful determinations of Schwartz and Kemp [27] have given the same results. In all

27. Schwartz, Karl; and Kemp, Herwig: Ueber den normalen Blutzuckergehalt beim Hunde und seine physiologische Schwankungen, Biochem. Ztschr. **194**:351 (Feb. 7) 1928.

dogs there was a sinking of the blood sugar values both at eighteen hours and at the end of another two days of starvation. The lowest figures were obtained from one to four months after the operation; after a while, a gradual rise took place, which approximately reached the preoperative values. The same wave of change in carbohydrate metabolism can be followed here as in our double sugar tolerance curves, as has been observed by two of us in our unpublished intraperitoneal tolerance curves.[16] On dog 33 which had been used for our double sugar tolerance curves, only a preoperative and two subsequent starva-

TABLE 2.—*The Effect of Starvation on the Blood Sugar Level Before and After Isolation of the Tail of the Pancreas* *

Dog	Fasting Period, Hours	Preoperative Values, Mg. per 100 Cc.	Date of Operation	Postoperative Values							
				9/24	10/25	11/17	12/4	12/27	1/14	1/30	2/19
26	24	101.5	7/27	90.9	75.2	79.4	85.4	74.0	71.5	80.0	85.1
	72	79.0	....	78.8	73.0	65.6	70.9	68.5	74.0	68.9	72.0
27	24	85.1	7/21	102.5	83.3	71.4	84.0	77.0	72.0	76.6	83.3
	72	79.3	....	81.6	58.3	66.6	70.0	60.0	68.0	67.1	68.0
28	24	90.7	8/23	76.9	81.0	68.9	71.4	78.0	71.5	72.5	74.0
	72	75.8	....	78.8	55.2	64.1	65.5	62.0	67.1	62.4	64.0
29	24	92.5	10/6	.....	....	82.5	82.6	71.4	....	88.8	74.0
	72	80.0	....	.....	....	59.0	60.0	66.0	....	66.6	66.0
30	24	89.2	12/1	.....	....	....	90.2	73.0	75.4	72.5	74.5
	72	75.4	....	.....	....	....	67.8	58.8	68.9	63.2	67.0
31	24	77.7	1/5	.....	....	....	....	....	72.0	82.0	81.0
	72	76.7	....	.....	....	....	....	....	74.0	64.5	65.0
32	24	77.0	1/5	.....	....	....	....	....	78.6	78.4	76.0
	72	58.8	....	.....	....	....	....	....	70.0	61.7	63.0
33	24	89.1	8/3	.....	....	65.0	....	....	....	....	83.6
	72	70.2	....	.....	....	39.5	....	....	....	....	81.2

* This tables illustrates the behavior of the blood sugar level after twenty-four and seventy-two hours of fasting. The dogs received as much water as they wanted and were not dehydrated, as checked by hemoglobin determinations. One preoperative determination and several postoperative determinations were made. The lowest figures following three days of fasting were obtained around the third month. In dog 33 a typical hypoglycemia with extreme fatigue, restlessness and tremor developed on the ninety-fifth day. This was relieved within a few minutes by a dose of dextrose The average lowest value was 57.5 mg. per hundred cubic centimeters of blood.

tion curves were obtained. Ninety-five days after the operation, the blood sugar during fasting was 65 mg. per hundred cubic centimeters of blood; twenty-four hours later, a reading of 41.3 mg. and a day later of 39.5 mg. of dextrose per hundred cubic centimeters of blood was made. The dog showed clinical symptoms of hypoglycemia, and was quickly relieved by dextrose. Two hundred and seventy-eight days later, the readings are close to the preoperative values. There was no change in the dog's weight and appearance during the whole experiment.

COMMENT

A study of our charts indicates that following the isolation of the tail of the pancreas in dogs a definite lowering of values during fasting

and a flattening of the curves took place in all five dogs. In dog 1, the lowest blood sugar level was encountered on the one hundred and sixth day; in dog 2 on the one hundred and thirty-sixth day; in dog 3 on the thirty-fifth day, in dog 4 on the twenty-seventh day and in dog 5 on the thirtieth day following operation. These blood sugar values during fasting are well below the lowest limit of normal, and are also well below the preoperative blood sugar levels of the same dogs. Schwartz and Kemp, in numerous determinations of the blood sugar of normal dogs during fasting, found very small fluctuations during a period of several months.[27]

There was also a change in the character of the sugar tolerance curves. They became flatter and not only reached the fasting level within two hours after the double injection of sugar, but frequently showed a posthyperglycemic dip.

The lower sugar values and flatter curves, however, did not persist at their almost hypoglycemic level, but later showed a gradual rise. In dogs 1, 2 and 5 the level on the one hundred and eighty-seventh, one hundred and thirty-sixth and seventy-ninth day, respectively, was still decidedly below the preoperative values; in dog 3 the tolerance curve was similar to the preoperative curve on the one hundred and sixty-fourth day, while dog 4 showed marked deterioration of the tolerance curve, showing the aspect of a diabetic curve.

With the exception of dog 4, all the dogs permitted the injection of a larger than normal quantity of dextrose at timed rates without developing glycosuria. These determinations were made between the one hundred and fifteenth and the one hundred and ninety-third postoperative days.

The blood sugar determinations on dogs fasting for more than two days showed an inability or at least a decreased faculty for maintaining blood sugar at its physiologic level for a certain time, after which a gradual return to preoperative values was observed.

The analysis of these observations must be undertaken with caution. It is true that hypoglycemia and flat tolerance curves immediately suggest an increased or uninhibited output of insulin from the pancreas. Following the case report of Wilder, Allan, Power and Robertson,[28] some other cases of hyperinsulinism were reported in man. One case report spoke of dysinsulinism relieved after the removal of a small tumor in the pancreas.[29] Our histologic observations, reported in a pre-

28. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, J. A. M. A. **89**:348 (July 30) 1927.

29. Howland, G.; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: Dysinsulinism, Convulsions and Coma Due to Islet Cell Tumor of the Pancreas, with Operation and Cure, J. A. M. A. **93**:674 (Aug. 31) 1929.

vious paper, also indicate a regeneration and hypertrophy of insular epithelium following retention of pancreatic juice; yet hypoglycemia of hepatic and adrenal origin must first be excluded. The inability to store glycogen in the diseased liver diffusely invaded by an adenocarcinoma has been seen by Nadler and Wolfer,[30] in which case a clinical picture almost identical to that of hyperinsulinism has been personally observed by one of us (de Takats). In order to be sure that our dogs were not suffering from a lack of glycogen storage, a few glycogen determinations were made from biopsy material obtained under anesthesia produced by procaine hydrochloride and a barbital derivative. From 4 to 6 per cent of glycogen was found in three of our dogs operated on at the time when they showed a low blood sugar level. One might even suspect, on the basis of Hetenyi's sugar determinations in tissues,[31] that an increased glycogen-fixation is present during insular hypoglycemia.

The reaction of the adrenals to this operation has been followed with great interest. The remarkable inversion of the epinephrine curve, which was observed at a certain period in two dogs, would indicate that the epinephrine hyperglycemia suddenly mobilized such an excess of insulin that the low blood sugar level of 52.6 mg. per hundred cubic centimeters of blood was reached half an hour after the injection. This low blood sugar in turn would mobilize endogenous epinephrine, as has always been maintained by Cannon, and this hyperglycemia would again call for insulin with a second dip to 47.9 mg. A remarkable imbalance of blood sugar regulation, which is temporary and is not observed in later epinephrine tests, suggests the possibility of changes in the nerve regulation of carbohydrate metabolism.

A number of workers maintain[32] that the interruption of sympathetic and parasympathetic fibers to the islets or to the liver produces changes in sugar tolerance. One is impressed with the abundance of nerve tissue in histologic sections of the pancreas. Some investigators might explain the results that we have observed on the basis of a partial denervating effect due to the separation of the tail from the body, but we believe that our observations are best explained by the histologic changes.

Omitting any tempting speculation, this much may be said of the effects of isolation of the tail of the pancreas on carbohydrate metabolism: A lowering of blood sugar values during fasting and an increase

30. Nadler, Walter H., and Wolfer, John A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, Arch. Int. Med. **44**:700 (Nov.) 1929.

31. Hetenyi, Geza: Experimentelle Untersuchungen über den Mechanismus der Insulin Wirkung, Ztschr. f. d. ges. exper. Med. **45**:440, 1925.

32. Pollak, Leo: Der Mechanismus der alimentären Hyperglykaemie, Arch. f. exper. Path. u. Pharmakol. **140**:1, 1929.

in sugar tolerance takes place. These changes occur from one to three months following the operation. Later these changes become less and less marked. In one dog, preoperative tolerance was observed and in another, a decrease in tolerance.

Several factors may be responsible for the return of the tolerance curves to normal or nearly normal. In the first place, our histologic studies, as well as those of others, have shown that the degree of sclerosis may later endanger the nutrition of the islets. A complete atrophy and sclerosis of the gland must sooner or later involve the islets. A type of diabetes may result as encountered following acute pancreatitis in man. This may have happened in dog 4. Hedon, Thirloix and Ivy and Farrell [33] observed a marked atrophy of the transplanted pancreas when it was not allowed to secrete externally. Jorns [15] laid great emphasis on the degree of sclerosis that may later endanger the function of the islets. In our earlier experiments, we noted that a double silk ligature with complete severance of the body from the tail would set up more edema and later sclerosis of the gland than a division with the cautery which permitted drainage of pancreatic juice, and which resulted in much less atrophy and fibrosis than a ligature. In this respect, the careful work of Jorns, who could show an improvement in sugar tolerance far more readily following a single ligature of the duct than after complete evulsion and permanent severing of the duct, is remarkable.

This takes us back to the original suggestion of Mansfeld, who used only a single massive ligature around the body of the gland. This is bound to permit the reestablishment of the continuity of the duct, which seems to favor the persistence of the islands after the initial stimulus of a mild pancreatitis has subsided.

One must also consider the fact, repeatedly observed by us at explorations following the operation on the pancreas, that not only the isolated tail of the pancreas, but the rest of the gland shows an edema and postoperative reaction. That an acute total pancreatitis with destruction of tissue may later lead to a hyperregeneration of islets must also be included in our possible interpretation of results. Allen [34] saw hypertrophic islets in his partial pancreatectomies. Fahr [35] performed gradual removal of the pancreas in several stages, and observed large islets as a response to increased functional activity of the remaining stump. Sprengel [36] reported a most instructive case, in which he saw the hemor-

33. Ivy, A. C., and Farrell, J. I.: Contributions to the Physiology of the Pancreas: I. A Method for the Subcutaneous Autotransplantation of the Tail of the Pancreas, Am. J. Physiol. **77**:474 (July) 1926.

34. Allen, F. M.: Glycosuria and Diabetes, Boston, W. M. Leonard, 1913.

35. Fahr, T.: Diabetes Studien, Virchows Arch. f. path. Anat. **215**:247, 1914.

36. Sprengell, H.: Klinische und anatomische Untersuchungen an ausgeheilten Pankreasfettnekrosen, Beitr. f. klin. Chir. **140**:117, 1927.

rhagic, edematous gland at operation and removed a large sequestrum of dead pancreatic tissue. Ten months later, when the patient died of intestinal obstruction, the pancreas showed numerous and large islands and only a slight fibrosis in its midportion, as a remnant of previous destruction. We could find no case reports of increased sugar tolerance in cases of healed acute pancreatitis, although shortly after the operation, low blood sugar values have been seen.[18]

It may be possible, then, that in our dogs a hyperregeneration of lost islets took place, which gradually subsided.

Another cause of the slowly subsiding hypoglycemia in dogs may be the effort of compensation in a normal animal. It is reasonable to assume that if hypoglycemia would develop following increased or uninhibited secretion of insulin, the mechanism which normally regulates a steady blood sugar level would attempt to restore the physiologic level. The experiments of Langecker,[37] who found definitely hypertrophic adrenal glands following the prolonged administration of insulin, are important in this connection. Gray and Feemster, who found compensatory hypertrophy and hypoplasia of the islets of a child born of a diabetic mother, described a hypertrophy of many medullary cells of the suprarenal glands.[38] The emergency theory of Cannon, McIver and Bliss,[39] could be applied perhaps to hypoglycemic states of longer duration. We have no proofs to offer for this suggestion. However, the tolerance curves in dog 1, which have been followed most closely, would indicate that steep rises and falls are observed on the one hundred and sixth and one hundred and eighteenth postoperative days, as if an increased sympathetic tonus of the vegetative nervous system were present. Also the epinephrine curves show a fluctuating response to this drug. Wohlgemuth and his co-workers spoke of a sympathicotonia following ligation of the duct in rabbits, but believed this to be the result of diminished antagonistic action of the islet cells on the adrenals.

The increased capacity to utilize ingested carbohydrate is not unknown in pancreatic diseases of man. Bergmann believes that in acute edema of the pancreas, which precedes acute necrosis, a lowering of blood sugar may be observed as a result of islet stimulation.[15] Jorns showed a tolerance curve of a patient three days after operation for

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37. Langecker, Hedwig: Der Einfluss chronischer Insulin-Zufuhr, auf die Nebennieren beim Kaninchen, Arch. f. exper. Path. u. Pharmakol. **134**:155, 1928.

38. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, Arch. Path. **1**:348 (March) 1926.

39. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XIII. A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924.

acute pancreatic necrosis, which showed a marked fall instead of a rise in the sugar level. Yet the blood sugar during fasting was 150 mg. per hundred cubic centimeters of blood. One can hardly suppress the suggestion that the ingestion of sugar in such cases sets up a reflex which fixes glycogen in the liver instead of mobilizing it, as it usually does. That this increase in glycogen fixation on a reflex basis may be the underlying cause of our low sugar levels and flat tolerance curves might also be considered, without postulating any increase in insulin action.

The increase in glycogen fixation, whether on a hormonal or on a nerve basis, would be desirable in diabetes. One theory of diabetes that has not been shattered by the discovery of insulin is founded on increased glycogen mobilization as a result of hyperirritability of the sympathetic nervous system. Whichever theory of diabetes is favored, a possible increase in glycogen fixation is worthy of a therapeutic attempt.

Such an operation in man should try to prevent a progressing sclerosis of the tail that would vitiate the initial results. In a case reported by one of us and Wilder [40] the gland was divided with the cautery to prevent too much retention and was wrapped in omentum with the hope of insuring better vascularization. Up to the present time—seven months after the operation—the improvement in sugar tolerance is still in progress.[41] We know far too little about the cause or causes of diabetes even to guess at the fate of regenerated islet cells. Would they be affected by the same agent that initially caused diabetes, or would their changed nerve supply protect them from inhibiting influences?

We have felt that the value of such an operation in man could be judged only by actual therapeutic attempts in juvenile diabetic patients whose power of regeneration is great, whose pancreas, particularly the blood vessels, is still intact, and who show remarkably scarce histologic evidence of insular lesions. A study of such cases in patients operated on carried over a period of years will help to decide this problem.

Our experiments on animals are suggestive enough to justify further trial in man, especially since it has been shown that the operation can be performed safely. The problem of handling the pancreatic stumps will be discussed elsewhere. The fact that in the normal dog the low sugar values are not persistent does not mean that the diabetic patient

40. De Takats, Geza; and Wilder, Russell M.: Isolation of the Tail of the Pancreas in a Diabetic Child, J. A. M. A. **93**:606 (Aug. 24) 1929.

41. Since this article has gone to press, another diabetic child has been operated on. Instead of using the division with the cautery, a strip of fascia lata was tied around the tail of the pancreas. Postoperative convalescence was smooth. Results of this operation will be published later.

might not be permanently benefited. While the performance of experiments on partially pancreatectomized dogs would seem tempting, we do not believe that the pancreatectomized dog is an ideal model for experiments for obtaining information concerning diabetes in man.

SUMMARY

1. In a series of five dogs, whose pancreas was divided with the electric cautery and then wrapped in omentum, double oral doses of sugar were given to test their sugar tolerance. Such tests repeated at intervals of from two to four weeks for several months showed a definite fall in blood sugar during fasting, a flattening of the tolerance curves and an increase in the posthyperglycemic hypoglycemia. In three of the five dogs, the lower levels still persisted at the conclusion of the experiment. One dog's values returned to normal, and one dog developed a definite decrease in tolerance.

2. Intravenous doses of dextrose at timed rates, carried out only once on each dog of this series showed that in four of five dogs a larger than normal amount of dextrose per hour per kilogram of body weight had to be given intravenously in order to produce glycosuria.

3. In dogs, fasting for from two to three days resulted in low amounts of blood sugar at a certain phase of the experiment; this phenomenon of "Karenzhypoglycemie of Mansfeld" was not permanent, and roughly followed the changes observed in the double sugar tolerance curves.

4. Blood sugar curves following the injection of epinephrine were determined three times in two animals, once before, once at the stage of lowest blood sugar values during fasting and once when the figures were returning toward normal values. A peculiar imbalance of carbohydrate regulation was reflected in these curves.

5. The correlation of these observations with our previous histologic studies would suggest the possibility that the mild pancreatitis set up by the stimulus of the operation results in a hypertrophy and hyperplasia of islet tissue, the functional activity of which is represented by the changes found in our present study. We are unable to say whether an actual increase in insulin output, a change in the secretory rate as a result of change in innervation or a functional liver block diminishing the outpour of glycogen is at play. Nor is it clear why these changes are not permanent. The possible causes for the return to the preoperative status of the normal dog are discussed.

6. It is emphasized that these results can by no means indicate the possible effects of such an operation on man. This question can be decided only by operations on patients with diabetes.